

THE AMERICAN HEART JOURNAL



©Am. Ht. Assn.

A JOURNAL FOR THE STUDY OF THE CIRCULATION

PUBLISHED MONTHLY

UNDER THE EDITORIAL DIRECTION OF
THE AMERICAN HEART ASSOCIATION

Fred M. Smith - - - - - Editor-in-Chief.

Associate Editors

Hugh McCulloch

Irving S. Wright

Horace M. Korns

Editorial Board

EDGAR V. ALLEN
CLAUDE S. BECK
HARRY GOLDBLATT
GEORGE HERRMANN
WILLIAM J. KERR
ROBERT L. LEVY
H. M. MARVIN

JONATHAN C. MEAKINS
ROY W. SCOTT
ISAAC STARR
J. MURRAY STEELE
PAUL D. WHITE
FRANK N. WILSON
CHARLES C. WOLFERTH

VOLUME 22
JULY—DECEMBER, 1941

ST. LOUIS
THE C. V. MOSBY COMPANY
1941

COPYRIGHT, 1941, BY THE C. V. MOSBY COMPANY

(All rights reserved)

Printed in the
United States of America

(R. R.)
L32m73:N25
H11

57528

Press of
The C. V. Mosby Company
St. Louis

The American Heart Journal

VOL. 22

JULY, 1941

No. 1

Original Communications

THE SYNDROME OF PAINFUL DISABILITY OF THE SHOULDER AND HAND COMPLICATING CORONARY OCCLUSION

JOHN MARTIN ASKEY, M.D.
LOS ANGELES, CALIF.

WE WISH to describe a syndrome of painful disability of both the shoulder and hand which persists for several months to one or two years after coronary occlusion. It seems clear that it is precipitated by coronary occlusion, inasmuch as only six of eighteen patients had had any previous upper extremity pain, and in these six the pain was markedly increased by the cardiac attack.

The syndrome of combined shoulder and hand disability has not been described, although we feel that it is not a rare sequel of coronary occlusion. Several cases in Ernstene's report¹ are, we believe, of this type. We do not refer to the left arm and hand pain after a paroxysm of angina pectoris, when the extremity is held immobile for fear of exciting more pain, but to a persistent, painful disability which is associated with restriction of shoulder movement and swelling of the fingers.

MATERIAL

We have observed twenty-two patients with this syndrome. The diagnosis of coronary occlusion was made in eighteen, and was confirmed by the electrocardiogram in fifteen. We have included four more with a diagnosis of long-standing angina pectoris. In all four there had been an unusually severe attack prior to the development of the shoulder and hand pain. Several of the eighteen had had repeated occlusions. There were eleven men and eleven women, ranging in age from 48 to 79.

THE SYNDROME

It is important to emphasize that the syndrome was coincident with, or occurred after, coronary occlusion or persistent angina pectoris; otherwise, it might be dismissed as a fortuitous event which was only to be expected in patients beyond the age of 40. Because of the rather uncertain

Received for publication Aug. 20, 1940.
From the Department of Medicine, University of Southern California School of Medicine.

nature of the whole symptom complex and its mechanism of production, we wish to describe the changes in detail.

The syndrome resembles that of acute or subacute periarthritis of one or both shoulders, followed, usually in days or weeks, by stiffness, pain, and swelling of one or both hands (Table I). The shoulder involvement is associated with painful restriction of arm abduction and external rotation.

The onset of the pain may coincide with the occlusion, and it may be of excruciating intensity, requiring morphine, with marked trapezial tenderness, or it may appear several weeks after the cardiac seizure, and be mild, localized to the deltoid area, and attributed, perhaps, to a hypodermic injection. In one case, the shoulder pain developed seven months after the occlusion. Those whose pain came weeks or months later usually first noticed distress on abduction, as in the act of putting on a coat. Either or both shoulders may be involved. This disability, which prevents abduction or external rotation, lasts, although gradually improving, for an average of six months. Within a few days or weeks, there appears a mild unilateral or bilateral pain in the hands, with stiffness and inability to close the hand. This stiffness grows quickly worse; the finger joints become swollen; and the skin becomes tense and glossy, with obliteration of the interphalangeal wrinkling. The hand, in severe cases, is fixed in extension. There is often a deep rose-red suffusion of the palms. Usually, there is pain only with an attempt to close the hand. The fingers are more stiff than painful. In one instance, however, there was exquisite tenderness of the hand, with constant burning pain which was made worse by heat and relieved by ice. A violaceous discoloration appeared on the palm, and both palm and dorsum developed an exfoliative rash.

In another case, that of a pediatrician, the appearance of the hands, with their swollen, tense joints, glossy skin, and purplish-red discoloration of the palms led the patient and a colleague to state "if these changes occurred in children, we would diagnose them as aerodynia."

These two cases suggested that the role of the sympathetic nerves was predominant. The more common type suggests merely a rather rapid development of arthritis, with a very gradual improvement.

The hand involvement subsequent to the shoulder pain is probably an extension of the syndrome of shoulder pain alone after coronary occlusion, as previously described.^{3, 4} A number of patients who were seen long after coronary occlusion and had had severe shoulder pain did not mention hand swelling and stiffness, but the fact that these symptoms occurred was elicited by questioning. I think that this occurs in many of those who supposedly have shoulder involvement alone, but is of minor degree and may be overlooked.

*The following report was not seen when this paper was written: Spillane, J. D., and White, Paul D.: *Brit. Heart J.* Atypical Pain in Angina Pectoris and Myocardial Infarction, April, 1940.

It is interesting that many patients, after a few months, develop distinct thickening of the palmar aponeurosis near the metacarpophalangeal junction, usually of the middle and ring fingers. The overlying skin is puckered and thick and resembles the early stage of Dupuytren's contracture. This was called to my attention by Dr. William Paul Thompson in two of his cases, and I have been able to find it in five others. The hardening fails to progress to contracture and has noticeably diminished in two cases. Its association with the syndrome seems to be definite and not fortuitous, although its significance is not clear.

The shoulder pain usually appeared first, but in five of twenty-two cases the hand pain preceded the shoulder pain by one to four months.

Both in the shoulder and hand the pain is relatively intractable and persists for months. Improvement is gradual; usually the shoulder pain leaves first, with slower improvement in the hand, in which the swelling and disability may completely or partially disappear. This may take months or one to two years. Of ten patients who were seen from fifteen months to two and a half years after occlusion (Table I), only two have completely recovered the function of their hands. In only two of twenty-two cases were joints other than the shoulders or hands involved after the occlusion. In one there was pain in the right hip, and, in the other, in both ankles.

A PAINFUL POINT

During the stage of shoulder pain, a point of localized tenderness was found in fifteen of sixteen cases in which pressure was exerted over the anterior border of the trapezius muscle upon the mesial angle of the superior border of the scapula. The more severe the shoulder pain, the more acutely tender was this point. It apparently corresponded to the site of trapezius branches of the cervical plexus. The brachial plexus was not acutely sensitive to pressure.

Libman, et al.,² have reported that the pain of subacromial bursitis may be relieved by pressure against the spine at the level of the angle of the jaw. In certain cases, Boas and Levy³ were able to relieve the shoulder pain which followed coronary occlusion by pressure on the brachial plexus. Edeiken and Wolferth⁴ described a "trigger zone over the upper border of the left scapula where pressure induced pain in the left shoulder and up over the left side of the neck."

In two cases in which shoulder pain developed simultaneously with the occlusion, we decided to attempt to relieve it by pressing over the painful trapezius. Pressure caused such agonizing pain that it could be applied only after the administration of evipal. Then it was applied over the painful point for three minutes. The relief of pain and limitation of motion were remarkable. In one case the relief was permanent; in the other the pain has returned on several occasions after overwork, and each time it has been relieved by pressure. In a third case, in which

TABLE I
ANALYSIS OF TWENTY-TWO CASES OF SHOULDER AND HAND DISABILITY COMPLICATING CORONARY ARTERY DISEASE

AGE	SEX	TIME BETWEEN OCCLUSION AND SHOULDER PAIN	TIME BETWEEN SHOULDER PAIN AND HAND PAIN	DURATION OF SHOULDER PAIN	DURATION OF HAND PAIN	ROENTGENOGRAPHIC CHANGES	PRESENT STATUS	TIME AFTER OCCLUSION
60	F	1 week	3 weeks	6 months	3 months	Osteoarthritis both acromioclavicular joints; demineralization both hands	Patient is at work as buyer; has return of shoulder pain when overworking, and is relieved by pressure over trapezius	2½ years
68	F	2 days	4 weeks	9 months	16 months	Osteoarthritis both acromioclavicular joints; both hands, advanced atrophic arthritis	Hands now can be nearly closed and are not painful. No return of shoulder pain	2 years
63	F	Immediate	Immediate	11 months	2 years	Osteoarthritis right acromioclavicular joint and both hands	Right hand still cannot be closed	2½ years
63	M	3 months	3 weeks	6 months	6 months	Osteoarthritis both acromioclavicular joints; both hands normal	No further shoulder or hand pain. Is back at work as steam engineer	15 months
47	M	Immediate	4 weeks	6 months	6 months	Roughened tuberosity both shoulders; no hand changes	Back at work as baker. No return of pain	1½ years
51	M	*	*	12 months	18 months	Calcified bursa right shoulder; no other roentgenograms made	Still some hand swelling and pain. Shoulder pain improved	2 years
48	F	2 months	Simultaneous	18 months	18 months	Demineralization left humerus, left hand	Still restriction of shoulder and hands, but much improved	2 years
57	M	6 weeks	4 weeks	18 months	22 months plus	Shoulders normal; both hands early atrophic arthritis	Hands slightly swollen, stiff and painful. Shoulder pain gone	2 years
54	M	4 weeks	1 week	1½ years	1½ years	No roentgenograms made	Died of second coronary thrombosis 1½ years after first	
62	M	3 months	1 week	4 months plus	4 months plus	Calcified bursa right shoulder; sharpened margins both hands	Not located	

	F	6 months	Coincident	6 months	6 months	Osteoarthritis both shoulders; moderate atrophic arthritis both hands	Not located	2 years
74	F			6 months	6 months	Osteoarthritis both shoulders; moderate atrophic arthritis both hands		
64	M	2 days	2 weeks	7 months	7 months	Right shoulder normal; no other roentgenograms made	Died of congestive heart failure 8 months after occlusion	
71	F	3 days	2 weeks	6 months	6 months	Osteoarthritis both shoulders, both hands	Shoulder pain gone. Right hand shows slight thickening of palmar fascia. Some stiffness	16 months
48	M	*	*	6 months	8 months	Shoulders normal; both hands early atrophic arthritis	Definite hardening of right palmar fascia. Stiffness of hands	16 months
71	M	7 months	5 weeks	2 months plus	2 months plus	Roughened tuberosity left humerus; no hand changes	Not located	
54	M	*	*	2 months	6 months	Acromioclavicular roughening; both hands early atrophic arthritis	Disability gone in both shoulders and hands	1 year
79	F	5 days	3 weeks	1 month	6 months plus	Shoulders normal; osteoarthritis both hands	Right hand cannot be closed. Shoulder pain gone. Thickening of palmar fascia	6 months
64	M	8 months constant angina	4 months	6 months	6 weeks	No abnormalities	Shoulder pain relieved surgically. Right hand still slightly stiff. Thickening of palmar fascia	6 months
66	F	5 years angina pectoris	2 weeks	6 months plus	6 months plus	Osteoarthritis right shoulder and hand	Still disabled with shoulder and hand. Left palmar fascia thickening	6 months
59	F	10 years angina pectoris	*	1 month	2 months plus	No shoulder changes. Both hands, osteoarthritis	Shoulder pain gone. Hands stiff	1 month
47	F	6 weeks	1 week	4 months plus	4 months plus	Normal	Shoulder pain present. Both hands stiff. Slight thickening right palmar fascia	4 months
53	F	8 years angina	*	3 months plus	2 months	Normal	Hands can be closed. Right palmar fascia thickened and hard	6 months

*Hand pain preceded shoulder pain.

pressure was applied one month after the development of the shoulder pain, there was partial relief.

In another case of pain in the shoulder of many months' duration, pressure gave no relief from the pain caused by abduction.

As most of the patients were seen a number of months after the onset of shoulder pain, when they had established disability of the shoulder and swelling of the hands, pressure was not attempted, although increased tenderness was found in all but one case. Hypersensitive persons are somewhat tender over this point, and it is important to disregard anything but marked tenderness.

It may be significant that, in this atypical syndrome with shoulder pain, the cervical plexus nerves are sensitive. We have not found this marked sensitivity in cases of coronary occlusion without shoulder pain. Edeiken and Wolferth's⁴ trigger zones over the scapula, which are associated with postocclusion shoulder pain, may also represent sensitized cervical plexus nerves. The significance of this observation is uncertain. We mention it merely so that it may be studied by others. The relief of the acute, excruciating pain in two cases was dramatic, but the explanation is obscure. We do not feel that the evipal was a factor.

LOCALIZATION OF JOINT INVOLVEMENT

Persistent pain and disability developed predominantly in the left shoulder and left hand in ten cases, in the right shoulder and hand in eleven cases, and in one there was no difference, i.e., both shoulders and both hands were equally involved. This high percentage of patients with right-sided involvement, which is contrary to the typical left-sided anginal radiation, suggested the possibility of pre-existing arthritis as an etiological factor. The occurrence of pain and swelling in the hand preceding the shoulder involvement in five cases was an additional feature. The role of coronary occlusion in precipitating the syndrome seemed definite.

PRE-EXISTING ARTHRITIS

Whether or not there was a pre-existing arthritis must be ascertained from the history and the interpretation of the roentgenograms. Five patients gave a history of previous pain in the shoulder, and in all of these cases it was mild. One gave a history of preceding hand involvement. She had had stiffness of the hands since undergoing a thyroideectomy eight years before. Of two others, one had had rheumatic fever at the age of 15 years, and the other had had mild osteoarthritis of both knees several years before. Fourteen gave no history of any previous joint trouble.

ROENTGENOLOGIC OBSERVATIONS

Roentgenograms were taken of both shoulders and both hands in nineteen cases, regardless of the site of the pain and disability. The discordance between clinical signs and symptoms and roentgenologic interpretations in the case of any one joint is well known.

Roentgenograms of both shoulders and both hands were made in nineteen cases; in sixteen of these cases there were bony changes in either the shoulders or hands. Several roentgenologists were asked to interpret the abnormalities, and their individual opinions concurred. Two other patients had single roentgenograms of the affected shoulder; one showed a calcific bursitis, and the other showed no change. In one case no roentgenologic examination was made. There was no absolute correlation between the degree of change and the side of greater involvement. Of the nine patients with predominantly left-sided pain, six had bilaterally equal or chiefly left-sided roentgenographic changes. Two showed more abnormalities on the right side than on the left.

Those with predominantly right-sided involvement showed, usually, roentgenologic changes in both shoulders.

The natural tendency for anginal radiation to be left sided makes any correlation difficult.

TREATMENT

Various measures were used in the treatment, and were directed chiefly at the relief of pain. Aside from the narcotics, they seemed of little value. Cobra venom, bee venom, large doses of thiamin, salicylates, and, in one case, a paravertebral alcohol injection of the first and second dorsal sympathetic ganglia had only a negligible effect. The patients who had foci of infection removed did no better than the others. In many cases, heat was intolerable in the early stages, but later, with massage, seemed to help the hands.

DISCUSSION

The important point in this syndrome, in my opinion, is the precipitating effect of coronary occlusion. Although the syndrome occurred in four cases in which only severe angina pectoris was diagnosed, there is a strong suspicion that unrecognized occlusion may have occurred.

The sequence of events seemed to be myocardial ischemia, cardiac pain, shoulder pain, and, later, hand pain.

Clinically, the manifestations in the hand were caused by a combination of sympathetic nerve disturbance and arthritis, with varying degrees of predominance of one or the other. With causalgia as a result of sympathetic nerve irritation, the skin of the hands becomes smooth, glossy, and bright red; this occurred in a number of our cases. Dupuytren's contracture is regarded by many neurologists as the result of dysfunction of the sympathetic nervous system.⁷ It was found in seven of ten of our patients who were examined for it.

The course of the hand disability, although it persisted in many cases for two years, was characteristic of neither long-standing rheumatoid arthritis nor osteoarthritis. The hands lacked the muscle atrophy of the former and the Herberden's nodes of the latter, and they gradually improved rather than becoming worse.

The shoulder pain was similar to that which occurs with periartthritis. Ordinary periartthritis is usually ascribed to trauma, infection, or a metabolic disturbance. Trauma and infection can be eliminated as precipitating factors following coronary occlusion. That the action of coronary occlusion in causing shoulder pain is causalgie has been suggested by Edeiken and Wolferth. The possibility of an accompanying cervical neuralgia was suggested in our cases by the apparent sensitization of cervical plexus nerves and by the relief that some of the patients obtained from pressure.

Miller⁶ has demonstrated accessory nerve pathways which may connect afferent pain stimuli from the heart and from the shoulder. We feel this can explain the mechanism of production of the syndrome. Afferent impulses from the shoulder enter the fourth, fifth, and sixth cervical ganglia. Accessory sympathetic cardiac afferent fibers may also enter at this level. This would explain the sensitiveness of the trapezius, which is innervated by the cervical plexus.

The significance of localized lesions in determining the radiation of cardiac pain stimuli has been emphasized by Boas and Levy.³ We feel that the difference in the syndromes, after coronary occlusion, of shoulder pain without restriction of movement, shoulder pain with restriction of movement, and shoulder pain plus hand involvement is probably one of degree and depends upon several factors.

The intensity of the cardiac afferent stimulus, the degree of joint involvement, and the sensitivity of the patient are probably determining factors.

It is difficult to say what the mechanism is, but the following deductions seem justifiable:

1. The painful shoulder and hand syndrome herein described is clearly a sequel of coronary occlusion. When it appears in connection with repeated attacks of angina pectoris, we believe that a "silent" occlusion should be suspected.

2. Latent arthritic changes are usually present in the shoulder and hand.

3. The process is self-limited and seems to be little affected by any type of therapy. Infection apparently plays a negligible role.

4. The syndrome seems to be the resultant of sympathetic nerve disturbance caused by myocardial ischemia and pre-existing shoulder and hand lesions.

REFERENCES

1. Ernstene, A. C.: Shoulder Pain as a Sequel to Myocardial Infarction, *Arch. Int. Med.* 66: 800, 1940.
2. Libman, E., Blumgart, H. L., et al.: Total Ablation of Thyroid in Angina Pectoris and Congestive Failure; Summary of Results in Treating 75 Patients During Last 18 Months, *J. A. M. A.* 104: 17, 1935. (Discussion by E. Libman, p. 25.)
3. Boas, E. P., and Levy, H.: Extracardiac Determination of Site and Radiation of Pain in Angina Pectoris With Special Reference to Shoulder Pain, *Am. Heart J.* 14: 540, 1937.

4. Edeiken, J., and Wolferth, C. C.: Persistent Pain in Shoulder Region Following Myocardial Infarction, *Am. J. M. Sc.* 191: 201, 1936.
5. Mackenzie, J.: Symptoms and Their Interpretations, London, 1909, Shaw & Sons, Ltd., p. 8.
6. Miller, H. R.: Angina Pectoris, Baltimore, 1939, Williams & Wilkins Company, p. 130.
7. Powers, H.: Dupuytren's Contracture 100 Years After Dupuytren: Its Interpretation, *Ment. Dis.* 80: 386, 1934.

DISCUSSION

DR. EMANUEL LIBMAN, New York.—This elaborate and well-prepared presentation of Dr. Askey's is a very welcome contribution. It is of particular interest to me, because in the interpretation which I will place upon it, and which, as he has intimated, he believes to be correct, it points again to what I have long believed to be the essential etiological factor in coronary artery disease and coronary thrombosis, namely, a diathetic metabolic disturbance, called the "gouty" state. This term is used to indicate a disorder of which we have no really definite knowledge, except that it is caused by hepatic dysfunction. The idea that a change in uric acid metabolism is the primary cause of "gout" or "goutiness" (atypical gout) is not now accepted by many clinical investigators. Some time ago I put forth the suggestion that an essential element is an abnormality of lipoid metabolism and that the uric acid disturbance probably arises secondarily. Interesting and important in this connection are publications during the last few years in which it was demonstrated that, in cases in which there had been typical attacks of "gout," the administration of a high-fat diet would bring on such attacks and that they were accompanied by an elevation of the uric acid content of the blood.

Dr. Askey has spoken of three possible explanations of the clinical picture to which his paper is devoted: (1) that it is entirely dependent upon the coronary thrombosis, (2) that it is the result of a metabolic disturbance, and (3) that it is caused by a combination of the first two mechanisms.

What evidence have we in favor of the possibility that the condition is of metabolic origin and not entirely dependent upon the state of the myocardium? Strong evidence is afforded by observations on patients who have suffered coronary occlusion with the pain limited entirely to the left side and then develop a shoulder disorder on the right side. Further evidence of the role of a metabolic disturbance was presented in two of the cases described today, in which there were symptoms in the right hip and right ankle.

The occurrence of Dupuytren's contraction, in my opinion, also points to a metabolic disturbance. In several cases of Dupuytren's contraction in "gouty" persons, I have been able to study the mechanism of its development. In these cases I found that the first thing to appear was fine nodules, such as one finds elsewhere in "gout," in the tendons. These gradually increased; fibrous tissue developed between them; and then the tendons became attached to the skin. Apparently, the development of this fibrous tissue is increased by movement of the tendons. I cannot exclude a partial role on the part of the nervous system. If you will study your own hands and other parts of the body (especially the upper parts of the legs)—I am referring to those over 40 years of age—you will find such nodules in the tendons, fascia, and periosteum. Some are loose and later may become attached.

The cases of coronary artery atherosclerosis and coronary thrombosis must be studied from another standpoint. One must investigate the frequency in the patients' histories of the occurrence of hemorrhoids, bursitis, furuncles, carbuncles, pruritis (especially pruritis ani), and a number of other features of the "gouty diathesis." Careful statistical study is essential because these conditions are rather common.

We know that directly after coronary occlusion there may be certain phenomena as a result of the myocardial necrosis. Such necrosis may cause fever, leucocytosis, temporary joint inflammation, and mild jaundice. In relation to Dr. Askey's studies, however, I wish to draw attention to the possibility of effects produced by myocardial ischemia as such. It is not generally realized that the myocardial ischemia can influence the autonomic nervous system and activate conditions that may have already existed, or to which a tendency was already present.

We have a hint of this in the occurrence of pyloric spasm with eructation, and other discomforts, in patients suffering from the results of coronary artery disease. Here we may find evidence of what I have called "rebounds in the autonomic nervous system." If the heart is under strain, whether because of fresh coronary occlusion or insufficiency resulting from coronary narrowing, many conditions may occur, for example, pylorospasm and cardiospasm. As a result there may be eructation, with relief from the cardiac pain. I am not at all convinced that this is simply the result of a release from "pressure of the gas on the heart." I am inclined to believe that relief of the secondary spasm or spasms improves the condition of the heart by improving the circulation or by bringing about a diminution in toniccity. I could cite many examples of such "rebounds."

I have not found it necessary to use any anesthetic or sedative in carrying out the manipulation for relieving shoulder pains. If one explains to the patient that the method is painful, that he will probably be very uncomfortable, but that it may be of use, he will practically always allow one to finish the treatment. If necessary, one can, by pressing on one of his own Erb's points, show that it is painful to everyone.

DR. ERNST P. BOAS, New York.—This most interesting presentation of Dr. Askey's is important because physicians are still not recognizing this syndrome. I can confirm all of the clinical observations made by Dr. Askey. I too have seen these palmar contractures. I have seen a number of cases in which the acute shoulder syndrome antedated the coronary occlusion, and others, as he pointed out, in which a diagnosis of coronary occlusion was made because of the sudden appearance of the shoulder pain.

The problem of the mechanism and cause of this shoulder condition is a most interesting one, and I am inclined to agree that there must be an underlying local predisposition; whether it is a diathesis in the sense meant by Dr. Libman or whether it is simply a local disturbance I do not know.

In my personal experience, the involved shoulder usually was the shoulder to which there was radiation of the anginal pain. I have seen exceptions, but the discrepancies were by no means as great as those observed by Dr. Askey.

I have seen a few cases in which this shoulder syndrome appeared after other types of cardiac attacks. I had two patients with paroxysmal auricular fibrillation and some with aortic stenosis who developed this shoulder syndrome.

Whether the trophic disturbances in the hand can be attributed to reflex involvement of the sympathetic nervous system as a result of the cardiac lesion, I do not know. After all, similar disturbances occur in the hand following peri-arthritis of the shoulder which has no relationship to heart disease. On the other hand, there are many features of this clinical picture which suggest a mechanism analogous to causalgia.

Some of the other symptoms of which patients with coronary disease complain, namely, the marked muscular weakness of the left arm, trophic disturbances, perhaps in the absence of shoulder pain, herpes zoster in the distribution of the anginal pain, the response to pressure on the nerves of the brachial plexus or of the cervical nerves, as pointed out originally by Dr. Libman, suggest that there is most probably a causalgia-like mechanism underlying these clinical manifestations.

For the present I think we must predicate that there are two factors involved. One is the local condition of the shoulder, and the other is the reflex mechanism initiated by the afferent bombardment of stimuli from the heart. Beyond that I fear we cannot go. But it is most important to recognize and to evaluate this syndrome which has been so well delineated by Dr. Askey.

DR. H. R. MILLER, New York.—Perhaps it is feasible to look upon the anginal pain which is referred to the shoulder, or to any other atypical area, for that matter, as a manifestation registered in an unusual dermatomic segment.

Dr. Askey's cases leave little room for doubt that the disturbance he describes is related to a disease or derangement of the cardiovascular apparatus. The onset was definitely associated with coronary occlusion; there is, therefore, sound reason to believe that his premise that the shoulder pain is not a mere coincidence is correct. When the heart is already compromised for one reason or another, and pain is registered in an abnormal zone, we can account for the location of the pain only on the probability of transmission of pain impulses along afferent fiber tracts which are not commonly involved.

In Dr. Askey's cases, it seems to me, the evidence is clear—one might even say that it permits of no other interpretation—that there is a participation of accessory cervical branches of the afferent fiber system.

From the shoulder region afferent somatic nerves make their entry into C 4, 5, and 6 cord levels. The cardiac impulses, on the other hand, are carried by the upper four thoracic and eighth cervical nerves to corresponding cord levels. Between these two regions of entry lie several cord segments.

The shoulder region can be brought into relation to the cardiac plexuses when impulses from the latter arrive either (1) at the C 4-6 cervical cord levels through the intervention of accessory sympathetic neurons, or (2) at the upper thoracic cord levels where accessory somatic cervical fibers from the shoulder have found an entry.

With regard to pain initiated in the shoulder and reflected into the cardiac region or precordium, this eventuality is perhaps better understood if one realizes that any extracardiac territory or organ in the body may precipitate the so-called anginal syndrome. In this respect, a diseased gall bladder is not rare, but herniation of the esophagus or a painful bursa or shoulder are equivalent loci.

The effect achieved by the impulses which reach the cord segments for the mediation of pain is probably the result of a summation of impulses, in this case from the shoulder and from the cardiac plexuses. For the purpose of discussion we may designate the stream of afferent extracardiac impulses as (a), and those originating in the cardiac apparatus as (b). Sometimes the extracardiac territory, as in the case of the severe kind of neuritis described by Lian and his pupil Boyer, is sufficient to set off the "explosion." The patient looks as if he were in the throes of an attack of coronary occlusion, whereas, in reality, he has engendered an overwhelming number of (a) impulses. In most cases the heart itself gives rise to a quantity of impulses sufficient to produce anginal pain. Arthritis or any other localized pathologic condition of the shoulder which was pre-existent or developed after a coronary occlusion would make it possible for impulses of pain to be transmitted from the heart or shoulder into "overlapping" cord segments.

DR. LIBMAN.—I should like to add a word concerning the pigmentation of which Dr. Askey spoke. How often did you note the pigmentation?

DR. ASKEY.—That was the only instance.

DR. LIBMAN.—Because of the reference which was made to the question of involvement of the autonomic nervous system in these cases, I should like to draw attention to the fact that such involvement is present in a variety of joint affections.

You will find it very well described in the small monograph published long ago (1889) by Spender. He described the early clinical manifestations of what he called osteoarthritis, by which he meant rheumatoid arthritis, and pointed out that not infrequently, before the patients develop the joint disturbance, sweating, burning, tachycardia, pigmentation, and a variety of other symptoms may be present. I originally learned of Spender's work from Dr. Osler's *Practice of Medicine*. You will find a reference to it in the earlier editions.

DR. ASKEY.—It was a privilege to have these three men discuss my paper.

It was Boas and Levy's article in the AMERICAN HEART JOURNAL several years ago, which I read at a time when I had my first puzzling case, that aroused by interest in this subject. Dr Libman has been stimulating since the time when he pointed out that pressure over the acromial nerves would relieve the pain of sub-acromial bursitis. I asked him why he hadn't published this observation, and he said that he did not know why it relieved the pain and that he did not want to get a lot of letters about it. His concept that there is a gouty diathesis, in the sense of a lipoid disturbance rather than a uric acid disturbance, is, I feel, correct. Several of my patients showed some roentgenographic changes in the hands which were suggestive of gout; but there were no other findings, and the blood uric acid was normal.

Dr. Miller's discussion of the nerve pathways which are concerned when shoulder pain occurs with coronary occlusion was especially helpful to me.

THE PHYSIOLOGIC ACTION OF OXYGEN AND CARBON DIOXIDE ON THE CORONARY CIRCULATION, AS SHOWN BY BLOOD GAS AND ELECTROCARDIOGRAPHIC STUDIES

ALVAN L. BARACH, M.D., AND ALFRED STEINER, M.D.,
WITH THE TECHNICAL ASSISTANCE OF
MORRIS ECKMAN, B.S., AND NORMAN MOLOMET, PH.D.
NEW YORK, N. Y.

THE effect of inhaling a mixture containing 12 per cent oxygen for twenty minutes is rarely noticed by most normal persons. Slight headache, vertigo, and a feeling of breathlessness may be experienced. The heart rate is increased, and the circulation time is shortened. In cases in which there is some impairment of the coronary circulation as a result of arteriosclerosis or narrowing of the mouths of the coronary arteries, the inhalation of low-oxygen mixtures frequently results in a profound disturbance of cardiac function. Precordial pain may occur,¹ and, at times, collapse, pulmonary edema, or shock; the arterial blood shows a diminished oxygen saturation, a decrease in carbon dioxide content, and a slight shift in pH toward the alkaline side.^{2, 3} The heart rate is generally elevated, with a more marked increase in pulmonary ventilation² and decrease in circulation time³ than takes place in normal subjects.

The electrocardiographic response to the inhalation of low-oxygen mixtures is generally less marked in normal subjects than in patients with coronary disease; lowering of the T wave and depression of the S-T segment are the characteristic changes.²⁻⁶

The inhalation of high-oxygen atmospheres has a physiologic action that is, in many instances, opposite to that of low-oxygen atmospheres. Thus, the precordial pain of coronary thrombosis can be relieved by the inhalation of a 50 per cent oxygen mixture,⁷ and recently was relieved in a more striking manner by the inhalation of pure oxygen.⁸ Patients with numerous seizures of anginal pain which persisted when they were at rest in bed became largely free from attacks after they were placed in an oxygen chamber.⁹ Furthermore, when acute coronary occlusion is followed by peripheral circulatory failure, the inhalation of a 50 per cent oxygen mixture has been shown to relieve these symptoms in some cases.¹⁰

Received for publication Aug. 14, 1940.

From the Research Service,* First Division, Welfare Hospital, Department of Hospitals, the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York City.

The authors wish to acknowledge the help of The Linde Air Products Co., the Mary W. Rumsey Fund, and the Josiah Macy Foundation, in support of this investigation.

*Formerly the Research Division for Chronic Disease.

The electrocardiographic effects of the inhalation of pure oxygen have recently been studied by the authors.¹¹ Normal persons generally showed no change; in a few subjects an increase in the height of the T wave was produced. In patients with coronary disease, however, the T wave frequently becomes elevated, and, when it was previously diphasic or depressed, the inhalation of pure oxygen frequently makes it upright or higher. These changes will be reported in full later in this article. The heart rate is decreased 4 to 6 beats per minute in most normal subjects by the inhalation of pure oxygen.

In summary, a diminished tension of oxygen in the arterial blood decisively impairs the function of the coronary circulation in patients with coronary disease; conversely, an increased tension of oxygen in the arterial blood improves the function of the coronary circulation when it has been previously damaged. In this investigation, the role of carbon dioxide in the regulation of the coronary circulation was studied by administering various combinations of oxygen and carbon dioxide, and by observing the blood gases, the pH, and the electrocardiographic response.

METHODS

The blood gas analyses and calculations of the pH were done by the method of Van Slyke and Neill.¹² The pulmonary ventilation was graphically recorded on a Tissot apparatus. The method of providing continuous inhalation of a constant gas mixture has been previously described.³

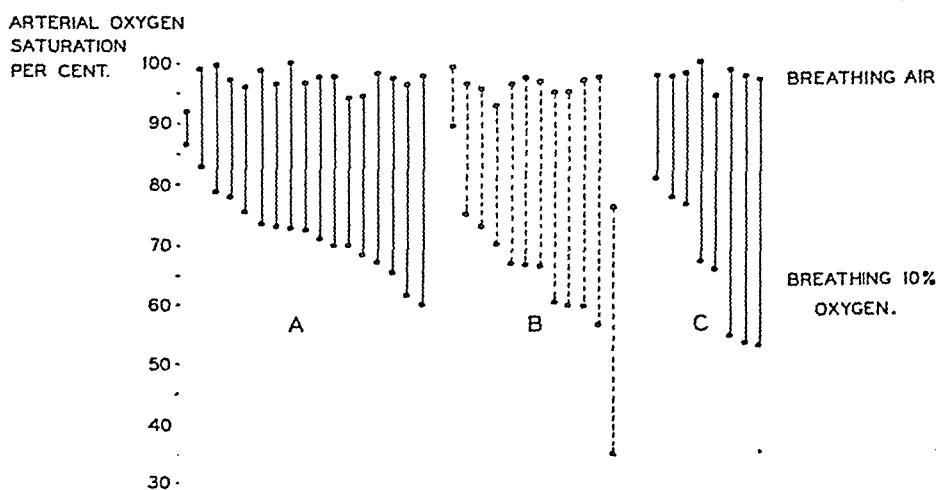


Chart I.—Fall in arterial oxygen saturation, induced by inhaling a 10 per cent oxygen atmosphere, in twenty-nine patients with heart disease and in eight normal subjects. *A*, Patients in whom cardiac pain was induced by inhaling the 10 per cent oxygen mixture. *B*, Patients in whom no cardiac pain was induced. *C*, Normal individuals. Each line represents one person.

RESULTS

The degree of arterial anoxemia which was produced in twenty-nine patients with heart disease and eight normal subjects as a result of inhaling a 10 per cent oxygen mixture for approximately twenty minutes

is shown in Chart I. There were nine cases of hypertensive vascular disease and twenty cases of coronary disease. The arterial oxygen saturation varied from 57 to 88 per cent, except in one case in which the unaccountably low figure of 35 per cent was encountered. In seventeen of twenty-nine patients in the cardiac group, precordial pain was produced by inhaling the 10 per cent oxygen mixture. The inhalation of the low oxygen mixture was stopped at the time the pain occurred, and, therefore, these patients breathed the mixture for a shorter period than those who did not experience pain. No significant difference in the degree of arterial anoxemia could be observed between these two groups, or between the cardiac and the normal group.

The effect of inhaling a 10 per cent oxygen mixture on the carbon dioxide content of arterial blood is shown in Chart II. A decrease in the arterial carbon dioxide content of approximately 2 to 5 volumes per cent took place in twenty-four patients with heart disease, thirteen of whom developed pain during the test, and in five normal subjects.

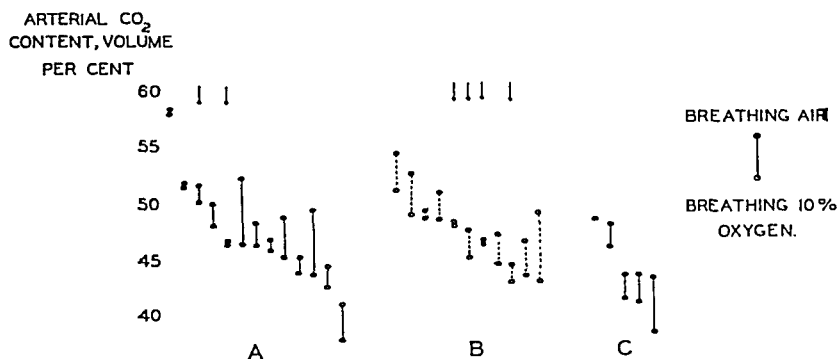


Chart II.—Fall in arterial carbon dioxide content induced by inhaling a 10 per cent oxygen atmosphere in twenty-four patients with heart disease and in five normal subjects. *A*, Patients in whom cardiac pain was induced by inhaling the 10 per cent oxygen mixture. *B*, Patients in whom no cardiac pain was induced. *C*, Normal individuals. Each line represents one individual. Arrows indicate cases in which the arterial CO_2 rose when 10 per cent oxygen was inhaled.

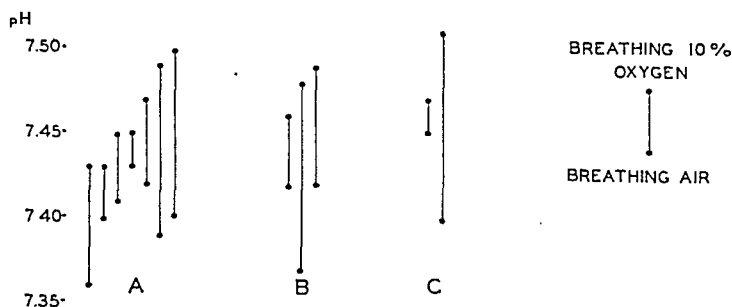


Chart III.—Rise in pH induced by inhaling a 10 per cent oxygen atmosphere, in ten patients with heart disease and in two normal subjects. *A*, Patients in whom cardiac pain was induced by inhaling the 10 per cent oxygen mixture. *B*, Patients in whom no cardiac pain was induced. *C*, Normal individual. Each line represents one person.

The pH of the arterial blood was ascertained in ten patients with heart disease and two normal subjects after the inhalation of a 10 per

cent oxygen mixture; the results are shown in Chart III. In seven cases precordial pain was initiated. The pH rose from 0.02 to 0.10; no difference was apparent between the two cardiac groups, or between the cardiac and the normal groups, but the series was admittedly small. It was apparent that overventilation due to acute anoxia lowered the free carbon dioxide of the blood to a greater degree than the combined carbon dioxide content, with a resultant increase in the alkalinity of the blood.

Electrocardiograms were taken of these patients before and at the conclusion of the period during which they inhaled the low oxygen mixture; no correlation between the degree of electrocardiographic change and the alteration in blood gas or pH equilibrium was observed.

The degree of alkaline shift in pH was in some cases so impressive as to suggest that alkalosis might play a role in the production of both the symptoms and the electrocardiographic changes of induced oxygen want. It is well known that alkalosis increases muscle and nerve irritability, at times to the point of tetany. Constriction of the capillary bed has been produced as a result of acute alkalosis, and, contrariwise, carbon dioxide administration has been followed by dilatation of these vessels.¹³⁻¹⁶ Direct observation of the pial vessels by Wolff and Lennox¹⁷ revealed that experimental alkalosis caused constriction, and acidosis produced by the inhalation of carbon dioxide resulted in dilatation of these vessels. The possibility presented itself that the coronary circulation would be affected in a similar way. It is interesting to note that petit mal attacks may be precipitated by inhaling low-oxygen mixtures, or by alkalosis produced by hyperventilation, and, conversely, that attacks of petit mal may be inhibited both by acidosis and increased oxygen tensions.^{18, 19} A further similarity between the effect of anoxia and alkalosis should be mentioned, namely, that not only is the T wave lowered by induced anoxemia, but also, to a very slight extent, by induced alkalosis.²⁰

The problem thus presented itself: Is the alkalosis that results from anoxia alone responsible either for spastic contraction of the coronary arteries or for constriction of the capillary bed? A new series of patients with heart disease and a group of normal subjects were then subjected to the induced anoxemia test, with and without the addition of small percentages of carbon dioxide. The presence of carbon dioxide in the low-oxygen mixture additionally stimulated respiration, and thereby produced a higher saturation of the arterial blood with oxygen than occurred when the low-oxygen atmosphere itself was breathed. In some cases, therefore, the effect of a 12 per cent oxygen atmosphere was compared to that of a 10 per cent oxygen and 3 per cent carbon dioxide mixture, and also a 10 per cent low-oxygen atmosphere to that of a 9 per cent oxygen with 2 or 3 per cent carbon dioxide mixture.

In Table I the electrocardiographic observations during inhalation of low-oxygen mixtures with and without the addition of carbon dioxide are summarized. Twenty-six tests were made on ten patients with heart disease, nine of whom were classified as having coronary sclerosis, two patients with miscellaneous disease, and eight normal subjects. The inhalation of a 10 to 12 per cent oxygen mixture in seven tests in the patient group resulted in significant changes in the electrocardiogram, such as lowering or inversion of the T wave or depression of the S-T segment. These changes, however, completely disappeared or were materially reduced when the same or a lower oxygen percentage was combined with 2 or 3 per cent carbon dioxide. In three patients no definite change took place with induced anoxemia, with or without carbon dioxide. In two patients the lowering of the T wave was slightly less marked during the inhalation of oxygen alone than when carbon dioxide was added, but in each instance the percentage of oxygen was lower when carbon dioxide was added. In six tests on normal subjects a definite lowering of the T wave was observed during inhalation of the low-oxygen mixture for a twenty-minute period; when 3 per cent carbon dioxide was added to the 10 per cent oxygen mixture, the T wave was normal. In tests on two additional normal persons there was no change either after inhalation of a 10 per cent oxygen mixture or a 10 per cent oxygen plus 3 per cent carbon dioxide mixture. The electrocardiographic changes induced by inhaling a mixture containing 10 per cent oxygen, and the effect of the addition of 3 per cent carbon dioxide on these changes are illustrated in Fig. 1.

In one case of coronary sclerosis, shock was induced by breathing a 10 per cent oxygen mixture for ten minutes; in four others precordial pain or distress was produced in a period of five to twenty minutes. In these five cases, inhalation of the same or lower concentrations of oxygen with 2 or 3 per cent carbon dioxide produced no symptoms whatsoever.*

In most cases of coronary disease, therefore, the addition of small percentages of carbon dioxide prevented or decreased the electrocardiographic effects of induced anoxemia. Before the results are interpreted, the blood gas analyses on some of these patients may be inspected. The blood was drawn after the electrocardiogram was taken, at the end of twenty minutes, unless pain occurred prior to that time. The data, which are shown in Table II, require detailed analysis.

In Case 1, the inhalation of a 9.3 per cent oxygen with 2 per cent carbon dioxide mixture resulted in an arterial oxygen saturation of 77.7 per cent, as compared to 68.5 per cent after the inhalation of a 10 per cent oxygen mixture without carbon dioxide; the pH was 7.46 after inhalation of the low-oxygen carbon dioxide mixture, and 7.52 after the low-oxygen mixture without carbon dioxide. Precordial distress

*The marked increase in ventilation was itself burdensome in the majority of cases.

TABLE I

ELECTROCARDIOGRAPHIC CHANGES DURING THE INHALATION OF 9 TO 12 PER CENT OXYGEN MIXTURES, WITH AND WITHOUT 2 TO 3 PER CENT CARBON DIOXIDE, IN CASES OF HEART DISEASE AND NEPHRITIS, AND NORMAL SUBJECTS

CASE NO.	DIAGNOSIS	DATE OF OBSERVATION (1940)	GAS MIXTURE BREATHED	ELECTROCARDIOGRAPHIC CHANGES	REMARKS
1	Coronary sclerosis	March 12	10% oxygen 10% oxygen, 3% carbon dioxide	T ₁ , T ₂ inverted; S-T ₂ , S-T ₃ depressed T ₁ , T ₂ upright; S-T ₂ , S-T ₃ not depressed	Precordial distress No distress
		April 1	10% oxygen 9.3% oxygen, 2% carbon dioxide	T ₁ inverted; T ₁ diphasic; S-T ₂ , S-T ₃ depressed T ₁ , T ₂ upright; S-T ₂ , S-T ₃ not depressed	Precordial distress No distress
		March 15	10% oxygen 10% oxygen, 3% carbon dioxide	T ₃ inverted; S-T ₄ markedly depressed T ₃ upright; S-T ₄ much less depressed	
		March 20	12% oxygen 10% oxygen, 2% carbon dioxide	S-T ₂ , S-T ₃ , S-T ₄ depressed; T ₃ lowered S-T ₂ not depressed; S-T ₃ , S-T ₄ much less depressed	
3	Coronary sclerosis	March 16	10% oxygen	T ₁ diphasic; T ₁ lowered	After 10 minutes pulse and blood pressure fell; patient went into shock
			10% oxygen, 3% carbon dioxide	T ₁ upright; T ₁ higher	Breathed this mixture for 20 minutes without symptoms
		April 5	10% oxygen 9% oxygen, 2% carbon dioxide	No definite changes No definite changes	Hyperventilation induced with 10% oxygen No symptoms
		March 17	10% oxygen 10% oxygen, 3% carbon dioxide	T ₁ , T ₂ , T ₄ lowered; S-T ₁ , S-T ₂ , S-T ₄ depressed S-T depression and lowering of T did not occur	Precordial pain No precordial pain

5	Coronary sclerosis	March 29	10% oxygen 9% oxygen, 3% carbon dioxide	T ₁ diphasic; S-T ₂ depressed No S-T ₃ depression; T ₄ more upright	
6	Coronary sclerosis and hypertensive vascular disease	April 12	10% oxygen 9% oxygen, 3% carbon dioxide	T ₁ , T ₃ lowered T ₂ , T ₃ , T ₄ higher	
7	Coronary sclerosis and hypertensive vascular disease	March 27	12% oxygen	No definite changes	Precordial pain occurred in 15 minutes
8	Hypertensive vascular disease	March 14	10% oxygen 10% oxygen, 3% carbon dioxide	No definite changes T ₁ , T ₂ lowered; T ₃ inverted T ₁ , T ₂ higher; T ₃ upright	Breathed mixture 20 minutes without symptoms
9	Coronary sclerosis and hypertensive vascular disease	April 22	12% oxygen 9% oxygen, 2% carbon dioxide	No definite changes No definite changes	
10	Coronary sclerosis?	April 17	10% oxygen 10% oxygen, 3% carbon dioxide	S-T ₁ depressed; T ₁ , T ₂ , T ₃ lowered; T ₄ diphasic S-T ₁ not depressed; T ₁ , T ₂ , T ₃ higher; T ₄ upright	Hyperventilation induced with 10% oxygen
		April 27	12% oxygen 9% oxygen, 3% carbon dioxide	T ₁ , T ₄ slightly lower T ₁ , T ₂ , T ₄ moderately lower	
		March 14	10% oxygen 10% oxygen, 3% carbon dioxide	T ₁ , T ₂ , T ₄ inverted T ₁ , T ₂ upright; T ₄ diphasic	
		March 25	12% oxygen 10% oxygen, 2% carbon dioxide	No definite changes No definite changes	
11	Chronic nephritis	April 8	10% oxygen 9% oxygen, 2% carbon dioxide	T ₁ , T ₂ , T ₃ , T ₄ lowered; T ₄ diphasic T ₃ , T ₄ diphasic	

TABLE I—CONT'D

CASE NO.	DIAGNOSIS	DATE OF OBSERVATION (1940)	GAS MIXTURE BREATHED	ELECTROCARDIOGRAPHIC CHANGES	REMARKS
12	Multiple sclerosis	March 18	10% oxygen 10% oxygen, 3% carbon dioxide	T ₁ flat T ₃ upright	
13	Normal	March 12	10% oxygen 10% oxygen, 3% carbon dioxide	T ₁ , T ₂ , T ₄ lowered T ₁ , T ₂ , T ₃ , T ₄ normal	
14	Normal	April 18	10% oxygen 10% oxygen, 3% carbon dioxide	T ₂ , T ₄ lowered T ₂ , T ₄ normal	
15	Normal	April 19	10% oxygen 10% oxygen, 3% carbon dioxide	T ₄ diphasic; T ₁ , T ₂ , T ₃ , T ₄ lowered T ₄ upright; T ₁ , T ₂ , T ₃ , T ₄ higher	10% oxygen and hyperventilation. Dizzy Comfortable
16	Normal	April 17	10% oxygen 10% oxygen, 3% carbon dioxide	T ₁ , T ₂ , T ₄ lowered Lowering of T ₁ , T ₂ , T ₄ not present	Hyperventilation induced with 10% oxygen. Dizzy, faint No symptoms
17	Normal	April 17	10% oxygen 10% oxygen, 3% carbon dioxide	T ₁ , T ₂ , T ₄ lowered T ₁ , T ₂ , T ₃ , T ₄ lowered	Dizzy Comfortable
18	Normal	April 19	10% oxygen 10% oxygen, 3% carbon dioxide	No definite changes No definite changes	Hyperventilation induced
19	Normal	April 17	10% oxygen 10% oxygen, 3% carbon dioxide	No definite changes No definite changes	Hyperventilation. Dizzy Comfortable
20	Normal	April 20	10% oxygen 10% oxygen, 3% carbon dioxide	T ₂ inverted; S-T ₂ depressed; T ₂ , T ₃ lower T ₂ upright; S-T ₂ not depressed; T ₄ higher	15-minute test

did not occur when the low-oxygen mixture with carbon dioxide was inhaled, but appeared when the low-oxygen mixture alone was inhaled. Similarly, the depression of the T wave and S-T segment which was produced by straight anoxemia was not present when carbon dioxide was added to an even lower oxygen mixture (the electrocardiographic changes are illustrated by the second test in Case 1, Table I).

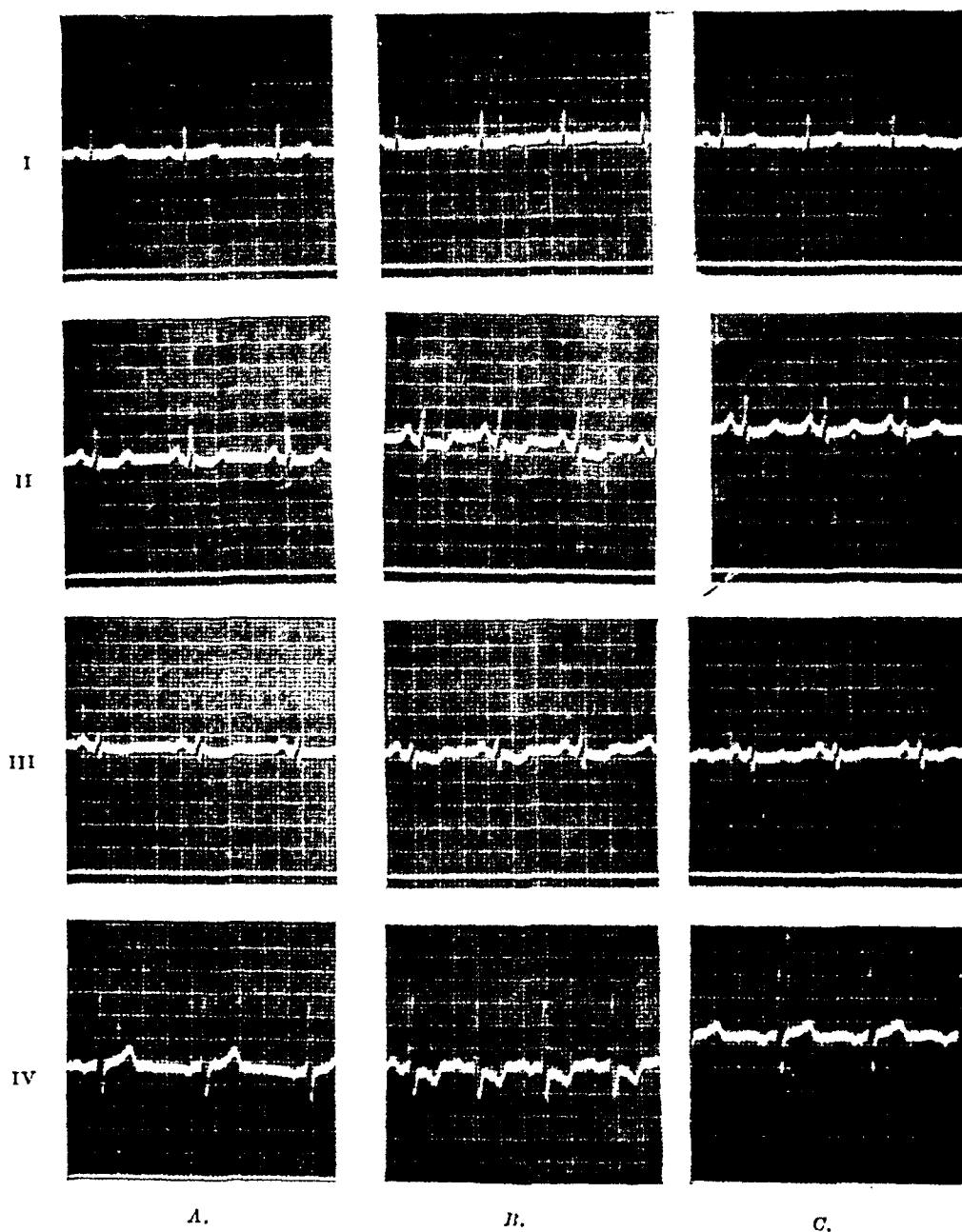


Fig. 1.—Electrocardiogram in Case 1. A, Control, T_1 upright, T_2 upright, T_3 diphasic, T_4 upright. B, After breathing a 10 per cent oxygen mixture for twenty minutes. T_1 upright but small, T_2 diphasic, S-T₂ depressed, T_3 diphasic, T_4 inverted, S-T₄ depressed. C, After breathing a mixture containing 10 per cent oxygen and 3 per cent carbon dioxide for twenty minutes. T_1 upright, T_2 upright, T_3 diphasic, T_4 upright; no S-T₂ or S-T₄ depression.

TABLE II
BLOOD GASES AND CLINICAL DATA AFTER INHALATION OF A 9 TO 12 PER CENT OXYGEN MIXTURE, WITH AND WITHOUT 2 TO 3 PER CENT CARBON DIOXIDE

CASE NO.	DATE (1940)	DIAGNOSIS	ARTERIAL OXYGEN			AIR-TERIAL CO ₂ CONTENT (VOL. %)	PH	GAS MIXTURE USED	PULMONARY VENTILATION (C.C. PER MIN.)	BLOOD PRESSURE		PULSE		REMARKS
			CON-TENT (VOL. %)	CAPAC-ITY (VOL. %)	SATUR-ATION (%)					START	END	START	END	
1	April 1	Coronary sele-rosis	15.3	19.7	77.7	53.1	7.46	9.3% O ₂ -2% CO ₂	12,000	140/100	156/100	80	90	No precordial dis-tress
2	March 20	Coronary sele-rosis and hy-pertensive vascular dis-case	13.5	19.7	68.5	50.6	7.52	10% O ₂	12,520	140/ 90	143/ 95	78	88	Precordial distress
			15.6	15.3	100.0	44.9	7.45	Air	12,520	180/100		64		
			12.3	16.6	74.1	47.6	7.50	12% O ₂	13,180	180/100	185/100	64	78	
			12.2	16.2	75.1	48.1	7.48	10% O ₂ -2% CO ₂	20,300	180/ 95	195/100	72	80	
3	April 5	Coronary sele-rosis	18.8	19.5	96.4	51.6	7.45	Air	5,410	120/ 80		86		
			14.7		73.2	49.8		9% O ₂ -2% CO ₂	15,030	145/ 90	140/ 90	92	88	
4	March 17	Coronary sele-rosis	17.4	20.1	86.5	41.0	7.60	10% O ₂	19,380	140/100	130/100	84	72	Hyperventilation induced
								-0% O ₂	8,900	130/ 56	144/ 94	76	86	Pain at 20 minutes
5	March 29	Coronary sele-rosis						10% O ₂ -3% CO ₂	12,790	132/ 60	135/ 70	60	76	No pain
			19.1	19.9	96.0	51.6	7.45	Air	8,770	210/110		72		
6	April 12	Coronary sele-rosis and hy-pertensive vascular dis-case	13.1	20.0	65.5	50.2	7.53	10% O ₂	12,780	205/110	230/120	76	80	Pain at 20 minutes
			16.5	20.5	80.5	52.0	7.46	9% O ₂ -3% CO ₂	18,720	230/130	230/130	72	64	No pain
			20.3	21.0	96.7	47.4	7.47	Air	5,400			112		
			18.5	21.9	84.5	51.5	7.44	9% O ₂ -3% CO ₂	14,700			102		
			17.7	21.9	80.8	45.3	7.54	10% O ₂	12,260			112	120	

7	March 27	Hypertensive vascular disease	18.8	19.1	98.4	49.1	7.42	Air	7,070	160/100	160/100	72	92	Pain at 15 minutes No pain
			15.3	19.5	78.5	48.1	7.43	12% O ₂	12,530	160/100	160/100	72	92	
			16.0	19.9	80.4	48.0	7.47	10% O ₂ , 2% CO ₂	17,340	155/100	185/110	72	84	
8	March 17	Syphilitic aortitis	15.5	15.7	98.7	54.7		Air	9,680	185/60	190/60			Pain at 5 minutes, Blood taken in 5 minutes
			12.4	16.3	76.1	48.9		10% O ₂						
			13.9	16.3	85.3	51.9		10% O ₂ , 3% CO ₂	12,520					Pain at 5 minutes, Blood taken in 5 minutes
9	April 22	Coronary sclerosis and hypertensive vascular disease	13.6	13.8	98.5	44.1	7.47	Air	6,590	170/110	175/110	84	92	
			10.7	14.2	75.4	45.0	7.48	12% O ₂ , 9% O ₂ , 2% CO ₂	10,940				98	
10	March 19	Coronary sclerosis and hypertensive vascular disease	14.7	15.1	97.3	34.6	7.47	Air	20,900	240/80	220/65	40	44	Blood taken in 15 minutes
			9.9	16.1	61.5	31.7		10% O ₂	38,630					
			12.4	15.9	78.0	32.4	7.44	10% O ₂ , 2% CO ₂						
11	March 25	Chronic nephritis	16.8	17.4	96.6	52.2	7.42	Air	7,180	135/100	135/100	80	100	
			12.8	17.1	74.9	52.4	7.47	12% O ₂	8,830	135/100	130/90	80	100	
			11.7	16.7	70.1	49.7	7.44	10% O ₂ , 2% CO ₂	9,760	130/90	145/90	80	92	
	April 8		11.9	16.7	70.1	49.7	7.44	9% O ₂ , 2% CO ₂	13,180	125/85	130/80	108	116	Hyperventilation induced
			11.5	17.3	67.5	49.3	7.55	10% O ₂	13,450	125/90	132/66	88	108	
12	April 23	Hypertensive vascular disease	18.0	18.4	97.9	51.0		Air		210/130	210/120	84	108	
			13.6	18.5	73.5	47.6		10.5% O ₂		250/140	210/120	100	108	
			16.4	18.6	88.2	50.8		10% O ₂ , 3% CO ₂		203/120	240/130			
			15.7	19.2	81.8	45.7		13% O ₂						
13	April 24	Coronary sclerosis?	16.6	17.2	96.5	51.2		Air		134/82	148/84	74	74	
			14.2	18.0	78.9	49.4		12% O ₂					74	
			14.7	18.0	81.7	51.1		9% O ₂ , 3% CO ₂		146/84	144/86	76	74	

If the arterial oxygen saturation in both experiments were precisely the same, the conclusion might be reached that the relative alkalosis which was present after inhaling the 10 per cent oxygen mixture was the significant factor in the production of both precordial pain and electrocardiographic changes. In that event, an assumption might be made that alkalosis had caused either contraction of the coronary arteries or constriction of the capillary bed, with progressive tissue ischemia and aggravated anoxia, and that these pathologic events were prevented by the inhalation of small amounts of carbon dioxide. Although an arterial oxygen saturation of 77.7 per cent represents severe anoxemia, which, in other cases of coronary disease, is sufficient to produce both precordial pain and electrocardiographic changes, the fact that this arterial oxygen saturation was higher than that which obtained when carbon dioxide was added makes possible the assumption that a more severe anoxemia might have been necessary to produce precordial pain and electrocardiographic changes in this particular case.

In Case 2, the arterial oxygen saturation was comparable in the two experiments, namely, 74.1 per cent after inhalation of a 12 per cent oxygen mixture, and 75.1 per cent after inhalation of a 10 per cent oxygen and 2 per cent carbon dioxide mixture. The pH was also higher after inhalation of a low oxygen mixture than it was after a low oxygen and carbon dioxide mixture, i.e., 7.50 as compared to 7.48. The presence of 2 per cent carbon dioxide did not completely prevent an alkaline shift, for the control pH was 7.45. Nevertheless, the electrocardiographic changes were much less after inhalation of the low-oxygen carbon dioxide mixture than after low oxygen alone (the electrocardiographic changes are shown in the second test in Case 2, Table I).

The interpretation of the results in this case appears to be that arterial anoxemia and alkalosis produced more marked electrocardiographic changes than anoxemia alone, and this suggests again that the alkaline shift caused by acute anoxia results in constriction of the capillary bed, additional ischemia, and progressive anoxia of the cardiac muscle. One other physiologic event must be borne in mind, namely, that alkalosis itself increases tissue anoxia, because oxygen is held more firmly to hemoglobin when the blood is more alkaline; thus, when a low-oxygen mixture is inhaled with carbon dioxide, more oxygen is liberated to the tissues even when the arterial oxygen saturation is identical in both cases. It must be admitted, therefore, that the oxygen tension of the cardiac muscle was higher when the low-oxygen carbon dioxide mixture was inhaled than when an even higher oxygen percentage was breathed without carbon dioxide. Conceivably, therefore, the more marked changes in the electrocardiogram caused by breathing the 12 per cent oxygen mixture, as compared to 10 per cent oxygen and 2 per cent carbon dioxide, may be explained by more severe tissue anoxia, without necessarily hypothesizing constriction of the capillary bed. However,

since alkalosis has been shown to produce constriction of capillaries in other parts of the body, it seems reasonable to assume that the same physiologic action may have exerted itself in the coronary circulation.

In Case 3, hyperventilation was induced while the patient was breathing a 10 per cent oxygen mixture; the pulmonary ventilation was 19,380 c.c. per minute, as compared to 15,030 when a 9 per cent oxygen and 2 per cent carbon dioxide mixture was breathed. No change was produced in the electrocardiogram by overventilation plus anoxemia, although the arterial carbon dioxide content fell from 51.6 to 41.0 volumes per cent and the pH increased from 7.45 to 7.60. The arterial oxygen saturation was relatively high, i.e., 86.5 per cent. The result in this case would suggest that alkalosis without severe anoxemia may be insufficient to produce precordial pain or electrocardiographic changes.

In Case 5, both precordial pain and electrocardiographic changes were produced by the inhalation of a 10 per cent oxygen mixture; these did not occur after inhalation of a 9 per cent oxygen and 3 per cent carbon dioxide mixture. The relative alkalosis produced by inhaling a 10 per cent oxygen mixture was prevented when carbon dioxide was added to an even lower oxygen mixture. However, increased pulmonary ventilation with the carbon dioxide mixture was associated with an arterial oxygen saturation of 80.5 per cent, as compared to 65.5 per cent when the 10 per cent oxygen mixture was breathed. As in Case 1, the higher oxygen tension of the arterial blood, rather than the more acid pH, may have accounted for the absence of symptoms.

In Case 6, the results were similar to those in Case 2, namely, with approximately comparable arterial oxygen saturations the electrocardiographic changes were more marked when a 10 per cent oxygen mixture was breathed, and the pH was 7.54, than when a 9 per cent oxygen and 3 per cent carbon dioxide mixture was inhaled, and the pH was 7.44.

In Case 7, with nearly comparable arterial oxygen saturations, precordial pain was experienced after the inhalation of a 12 per cent oxygen mixture, and not after 9 per cent oxygen with 2.5 per cent carbon dioxide.

In Case 8, a patient with syphilitic aortitis, pain was induced at the end of five minutes, both after the inhalation of a 10 per cent oxygen mixture and 10 per cent oxygen with 3 per cent carbon dioxide. In the latter experiment, the arterial oxygen saturation was 85.3 per cent, with an arterial carbon dioxide content of 51.9 volumes per cent; in the former (10 per cent oxygen), the arterial oxygen saturation was 76.1 per cent, with a carbon dioxide content of 48.9 volumes per cent. In other words, with constriction presumably present at the mouths of the coronary arteries, pain came on quickly irrespective of the blood gas changes. In a previous report³ it was noted that pain came on quickly in two cases of aortic stenosis, and in these cases the circulation time was not short-

ened. In most other cases of heart disease the circulation time was appreciably faster after the inhalation of a 12 per cent oxygen mixture.

In Cases 9 to 13 the blood gas changes could not be significantly correlated with clinical or electrocardiographic observations except in the last test in Case 11, in which there were less marked electrocardiographic alterations with a low-oxygen carbon dioxide mixture than with low oxygen alone; the arterial oxygen saturations were approximately comparable, and there was an alkaline shift of the pH during the inhalation of the low-oxygen mixture.

The blood pressure and the pulse rate showed no significant changes as a result of inhaling low-oxygen mixtures, either with or without carbon dioxide. In some cases the pulse rate was elevated. The pulmonary ventilation was markedly increased as a result of addition of small percentages of carbon dioxide in all cases except Case 1.

Before discussing the physiologic significance of the above results, the effect on the electrocardiogram of inhaling (1) pure oxygen, and (2) a mixture of 97 to 96 per cent oxygen and 3 to 4 per cent carbon dioxide should be presented (Table III). Observations were made on thirty-two patients who had primary heart disease, or whose cardiac function was affected by pulmonary or other disease. There were six normal and two miscellaneous subjects.

Of the thirty-two subjects in the cardiac group, twenty-five responded to the inhalation of either pure oxygen, or a mixture of 97 to 96 per cent oxygen and 3 to 4 per cent carbon dioxide, with either elevation of the T wave in one or more of the four leads, less inversion of the T wave, or a change from a diphasic to an upright T wave. In five cases there was no change after inhalation of either oxygen or oxygen with carbon dioxide. In one case, T_1 was very slightly lower after both tests, and, in another instance, T_3 was very slightly lower after oxygen and very slightly higher after oxygen with carbon dioxide.

In Table III an elevation of the T wave of 0.5 mm. ± 0.25 mm. is noted as +; an elevation of 1.0 mm. ± 0.25 mm. is noted as ++; an elevation of 1.5 mm. ± 0.25 mm. is noted as +++; and an elevation of 2 mm. is noted as ++++.

Of twenty cases in which the electrocardiographic changes caused by pure oxygen were compared with those which resulted from oxygen plus carbon dioxide, there were seven in which the T-wave elevation was higher with pure oxygen, one in which it was very slightly higher with the oxygen plus carbon dioxide mixture, and twelve in which the result was approximately the same. In the twelve instances in which the elevation of the T wave was noted as being equal after the two tests, the impression was frequently gained that there was very slight lowering of the T wave when carbon dioxide was added to the oxygen mixture. It was believed, however, that changes of a magnitude of 0.25 mm. were too small to be considered significant.

TABLE III

EFFECT OF INHALATION OF PURE OXYGEN AND OF A HIGH OXYGEN LOW CARBON DIOXIDE MIXTURE ON THE FORM OF THE ELECTROCARDIOGRAM

CASE NO.	DIAGNOSIS	ELECTROCARDIOGRAPHIC CHANGES AFTER 20 MINUTES' INHALATION OF	
		PURE OXYGEN	96% OXYGEN WITH 4% CO ₂
1	Coronary sclerosis Second test	T ₄ higher, + T ₄ higher, +++	T ₄ higher, +*
2	Pulmonary emphysema Second test	T ₃ higher, ++ T ₂ higher, ++	T ₃ higher, + T ₃ higher, +
3	Arteriosclerotic heart disease	T ₄ higher, +; T ₁ , T ₂ , previously diphasic, upright	T ₄ higher, +; T ₁ , T ₂ , previously diphasic, upright
4	Arteriosclerotic heart disease	No change	No change
5	Hypertensive vascular disease and cardiac insufficiency	T ₁ , T ₂ less diphasic; T ₄ previously inverted, upright	T ₁ , T ₂ less diphasic; T ₄ previously inverted, upright
6	Pulmonary fibrosis	T ₂ , previously diphasic, upright	T ₂ , previously diphasic, upright
7	Coronary sclerosis		T ₂ less inverted; T ₄ higher*
8	Coarctation of aorta	T ₄ higher, ++	T ₄ higher, +
9	Coronary sclerosis?	T ₄ higher, +	T ₄ higher, +
10	Hyperthyroidism	T ₄ , previously diphasic, higher, +	T ₄ , previously diphasic, higher, +
11	Coronary occlusion	T ₄ higher, ++	T ₄ higher, +
12	Coronary sclerosis	T ₁ , T ₄ less inverted	T ₁ , T ₄ less inverted
13	Arteriosclerotic heart disease	T ₄ higher, ++; T ₃ lower, -	T ₄ higher, +; T ₃ lower, -; T ₁ less inverted
14	Hypertensive vascular disease	No change	No change
15	Coronary sclerosis	T ₁ less inverted; T ₂ higher, ++	T ₂ higher, +
16	Coronary occlusion	No change	T ₃ higher, +
17	Splenic vein thrombophlebitis	T ₃ higher, ++; T ₄ higher, +++	T ₃ higher, +; T ₄ higher, ++
18	Beck's sarcoid	T ₁ , T ₂ higher, ++; T ₄ less inverted	T ₁ , T ₂ higher, +; T ₄ less inverted
19	Coronary sclerosis		T ₃ previously diphasic, upright; T ₂ , T ₄ higher, ++
	Second test	No change	No change
20	Coronary sclerosis	T ₃ slightly lower, -	T ₃ higher, +*
21	Coronary thrombosis	T ₁ lower, -	T ₁ lower, -
22	Coronary sclerosis	T ₄ higher, ++	T ₄ higher, +
23	Arteriosclerotic heart disease	T ₃ less inverted	Questionable change*
24	Hypertensive vascular disease	T ₄ higher, ++ T ₁ , T ₂ less inverted	T ₄ higher, +; T ₁ , T ₂ less inverted
25	Coronary sclerosis	T ₁ , T ₂ higher, +; T ₄ higher, ++	T ₁ , T ₂ higher, +; T ₃ higher, +
26	Tuberculous pericarditis	T ₂ , T ₄ higher, +	T ₂ higher, +

TABLE III—CONT'D

CASE NO.	DIAGNOSIS	ELECTROCARDIOGRAPHIC CHANGES AFTER 20 MINUTES' INHALATION OF	
		PURE OXYGEN	96% OXYGEN WITH 4% CO ₂
27	Intermittent claudication	No change	No change
28	Asthma	No change	No change*
29	Coronary sclerosis	T ₁ higher, + T ₂ higher, ++ T ₃ higher, + T ₄ higher, +	
	Second test†	T ₁ higher, + T ₂ higher, ++++ T ₄ higher, +	
30	Hypertensive cardiac vascular disease	T ₁ higher, +	
	Second test†	T ₁ higher, ++ T ₂ higher, ++	
31	Coronary sclerosis	T ₁ higher, ++ T ₂ higher, ++ T ₄ higher, +	
32	Acute infarction of anterior surface of the heart	No change	
	Second test†	T ₂ higher, +	
33	Coronary sclerosis	T ₄ higher, ++	
	Second test†	T ₁ higher, + T ₄ higher, +++	
34	Hypertensive cardiac vascular disease	T ₄ higher, ++	
	Second test†	T ₄ higher, ++++	
35	Normal	No change	No change
36	Normal	No change	No change
37	Normal	No change	T ₂ lower, -
38	Normal	No change	No change
39	Normal	T ₁ , T ₂ higher, ++; T ₃ , T ₄ higher, ++++	T ₁ , T ₂ , T ₃ , T ₄ higher, +
	Second test	T ₂ , T ₃ higher, ++; T ₄ higher, ++++	T ₂ , T ₃ , T ₄ higher, +*
40	Normal	T ₂ higher, ++	T ₁ , T ₄ lower, -

*97 per cent oxygen with 3 per cent carbon dioxide was used.

†Patient under intermittent oxygen treatment.

‡After 30 minutes of pure oxygen.

In the group of two cases of miscellaneous disease and six normal persons there was no change as the result of inhaling pure oxygen in six cases, and elevation of the T wave in two cases. In four of five cases in the group no change resulted from inhalation of the oxygen carbon dioxide mixture in 4; elevation of the T wave occurred in one, and lowering in two. The changes were less frequent in the control group, but in one instance there was definite elevation of the T wave in all four leads, and slightly less marked T-wave elevation after inhalation of the oxygen carbon dioxide mixture. An illustration of the effect of pure oxygen on the electrocardiogram is shown in Fig. 2. It will be observed that the T waves in Leads I, II, and IV are of greater amplitude than in the control tracing.

COMMENT

The induction of acute anoxia in patients with heart disease has been shown to produce overbreathing, a decrease in arterial carbon dioxide, and a shift in pH toward the alkaline side. To counteract the loss of

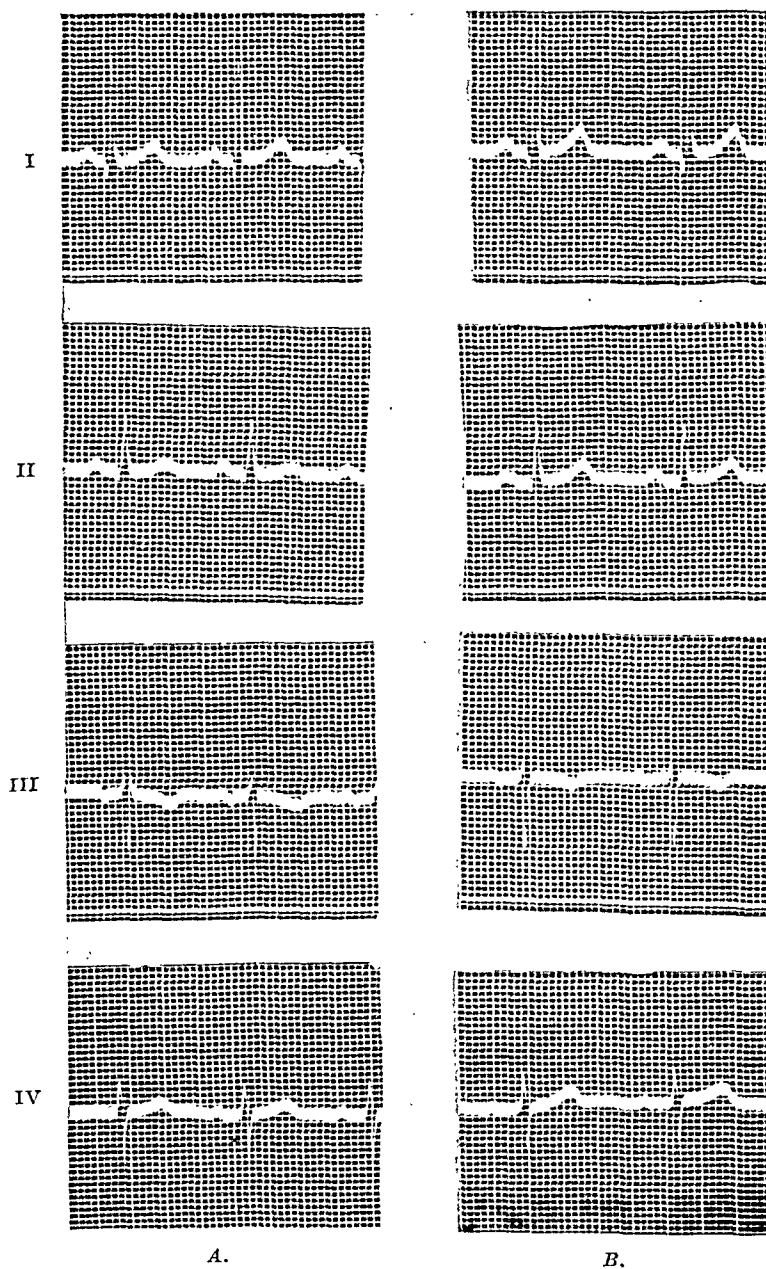


Fig. 2.—Electrocardiogram in Case 31. *A*, Control. *B*, After breathing pure oxygen for fifteen minutes. T_1 , T_2 are 1 mm. higher than the control, and T_4 is 0.5 mm. higher.

carbon dioxide, low-oxygen mixtures were inhaled with the addition of 2 to 3 per cent carbon dioxide. This procedure compensated for the undue elimination of carbon dioxide which overbreathing otherwise

produced, and prevented or decreased the alkaline shift of the blood pH. The stimulating effect of carbon dioxide on the volume of ventilation increased the arterial oxygen saturation above that which was found when a similar oxygen concentration was inhaled with carbon dioxide. In order to ascertain whether alkalosis played a role in the causation of the clinical and electrocardiographic changes of induced oxygen want, an attempt was made to produce a similar degree of arterial anoxemia in patients who had an alkaline shift in pH and in patients in whom such a shift had been prevented by carbon dioxide in the low-oxygen mixture. This was done by lowering the oxygen percentage of the mixture in which carbon dioxide was employed.

When symptoms or electrocardiographic changes resulted from inhalation of a 10 to 12 per cent oxygen mixture, repetition of the test with the addition of 2 to 3 per cent carbon dioxide prevented these changes in the majority of patients with coronary disease. In most of the cases (eight out of twelve), the arterial oxygen saturation was somewhat higher when carbon dioxide was employed. In four cases, however, in which the degree of arterial anoxemia was made comparable by administering less oxygen with the carbon dioxide than with the plain low-oxygen mixture, either no symptoms occurred or the electrocardiographic changes were less marked, in the patients who received carbon dioxide, and, therefore, in the cases in which an undue loss of carbon dioxide and alkaline shift in pH were prevented.

These results suggest that the alkalosis of induced anoxemia may be a factor in impairing the coronary circulation, either by causing constriction of the capillary bed or possibly by increasing the tendency toward coronary spasm. Since vasoconstriction of capillaries has been reported as the result of loss of carbon dioxide from the circulating blood, induced oxygen want in patients with coronary disease may be followed by a vicious train of pathologicophysiology events: arterial anoxemia, hyperventilation, loss of dissolved carbon dioxide, alkaline shift of blood pH, capillary (or possibly coronary) blood vessel constriction, ischemia, and progressive tissue anoxia. It is altogether likely that tissue oxygen want is the ultimate significant factor in the causation of the symptoms and signs of coronary insufficiency. Although tetany can be produced by hyperventilation in normal subjects, it will not occur if the hyperventilation is conducted during the breathing of pure oxygen. In other words, alkalosis in the presence of a high oxygen tension is not productive of tetany.

In a study by Kerr, et al.,²¹ hyperventilation was used to produce anxiety states and psychoneurotic symptoms. Among their cases was a patient with coronary disease who developed precordial pain after hyperventilation. In three of our cases of coronary sclerosis, hyperventilation for twenty minutes failed to produce precordial pain or electrocardiographic changes. In one case, hyperventilation was induced

with a 10 per cent oxygen mixture, and, although the pH shifted from 7.45 to 7.60, no precordial pain or electrocardiographic changes took place; the arterial oxygen saturation in this case was elevated as a result of increasing the volume of ventilation to 86.5 per cent.

These results suggest that hyperventilation is more likely to be harmful when it is combined with severe anoxemia. In the case of syphilitic aortitis, pain occurred promptly after five minutes of inhaling the low-oxygen mixture, whether or not it contained 3 per cent carbon dioxide. In this instance, constriction of the capillary bed or contraction of the wall of the coronary arteries was evidently not involved, for carbon dioxide exerted no effect; narrowing of the mouths of the coronary arteries presumably produced a type of constriction that could not be compensated for by increased diameter of the coronary or smaller peripheral blood vessels. In other words, the ischemia was not appreciably influenced by the addition of carbon dioxide, even though the arterial anoxemia was diminished (85.3 per cent, as compared to 76.1 per cent when the 10 per cent oxygen mixture was inhaled without carbon dioxide). The fact that the increased oxygen tension in the blood when carbon dioxide was added did not delay the time of appearance of precordial pain indicates the importance of ischemia as a factor in coronary insufficiency (i.e., in the case of constriction at the mouths of the coronary arteries); conversely, the prevention of the symptoms of coronary insufficiency by adding 2 to 3 per cent carbon dioxide to the low-oxygen mixture in cases of coronary sclerosis suggests that loss of dissolved carbon dioxide is of importance in the regulation of the circulation through the coronary arteries and the tissue capillaries.

Since the inhalation of carbon dioxide had the beneficial effects which have been discussed, the effect of a mixture of 2 to 3 per cent carbon dioxide and 98 to 97 per cent oxygen was tried clinically, with respect to its effect on the electrocardiogram.¹¹ There are insufficient data to draw a conclusion at this time; however, it was observed that the T wave was elevated by inhaling the above mixtures, although generally not to the extent produced by the inhalation of pure oxygen. An explanation of these results was suggested by Macleod in a conversation concerning the physiologic significance of the changes we had found. The studies of Wilson, Macleod, and Barker²² and later studies of Macleod²³ led to the opinion that a prolongation of the recovery period of cardiac muscle, with a delay in the oxidation of the products of metabolism, was one of the factors responsible for lowering of the T wave. According to this thesis, the inhalation of low-oxygen mixtures might delay the oxidation of products of metabolism. The addition of CO₂ to the low-oxygen mixtures would result in a lessening of tissue anoxia by preventing alkalosis, constriction of the capillary bed, and ischemia. In addition, the more acid pH of the blood, carrying an increased carbon dioxide tension, would unload oxygen into the tissues at a lower oxygen satura-

tion than blood in a more alkaline state. The T wave, therefore, was more upright, since tissue anoxia was relieved in some degree. Macleod's explanation may also apply to the occurrence of an elevation of the T wave during inhalation of pure oxygen in certain cases of coronary sclerosis; the increased oxygen tension may shorten the recovery period of cardiac muscle that might previously have been exposed to ischemic conditions. Admittedly, many other influences modify the height of the T wave, such as heat and cold,²⁴ and it is not the intention of this paper to offer a complete explanation of the mechanism of the T-wave deflection. That the tension of oxygen in the blood entering cardiac muscle was a determining factor in the direction and height of the T wave was an occurrence for which we sought an explanation; the clue given us by Macleod seemed consistent not only with our results, but with what is generally known in respect to the function of oxygen in muscle physiology.

SUMMARY

By means of blood gas and electrocardiographic observations, the physiologic action of oxygen and carbon dioxide on the coronary circulation was studied. When a deficiency of oxygen has been produced in the arterial blood by decreasing the oxygen concentration of inspired air, certain compensating mechanisms become manifest, such as an increase in pulmonary ventilation and circulation velocity. In cases of coronary sclerosis, the narrowed lumina of the coronary arteries impose a variable degree of obstruction to an increase in the flow of blood. The induction of oxygen want in the presence of this relative ischemia results in severe anoxia of the heart muscle, the consequences of which are (1) coronary insufficiency, with precordial pain and cardiac or peripheral circulatory failure, and (2) electrocardiographic changes, particularly lowering of the T wave or depression of the S-T segment.

The increased pulmonary ventilation produced by acute anoxia engenders a disproportionate loss of dissolved carbon dioxide, with a shift in blood pH toward the alkaline side. Since alkalosis produced by hyperventilation has been shown to cause constriction of capillaries in other parts of the body, the possibility that it may have the same effect on the coronary circulation was investigated. The addition of small amounts of carbon dioxide, such as 2 to 3 per cent, to a low-oxygen mixture prevented the clinical and electrocardiographic signs of coronary insufficiency which have been described above. Although the inhalation of a low-oxygen carbon dioxide mixture in eight out of ten cases of coronary disease resulted in a higher arterial oxygen saturation than the inhalation of a comparable low-oxygen mixture, there were four cases in which the symptoms or electrocardiographic signs of coronary insufficiency either did not occur, or were diminished, in the presence of a comparable, severe arterial anoxemia, when carbon dioxide loss was prevented.

The inhalation of high-oxygen concentrations is known to improve the function of the coronary circulation when it has been previously impaired. The electrocardiographic effects of the inhalation of approximately pure oxygen in thirty-two cases of coronary disease were studied. In twenty-seven cases, the T wave was rendered more upright. The addition of carbon dioxide to high-oxygen concentrations either had no effect, or, in six cases, diminished slightly the T-wave elevation produced by inhaling high-oxygen mixtures.

Accepting Macleod's thesis that one of the factors influencing the height of the T wave is the speed of recovery of cardiac muscle, we tentatively conclude that the evidence obtained in these studies suggests that the inhalation of low-oxygen mixtures prolongs the recovery period of heart muscle in patients with coronary disease, and that the inhalation of high-oxygen mixtures shortens the recovery period. In the presence of acute anoxia, the inhalation of small amounts of carbon dioxide shortens the recovery period of cardiac muscle, in part by increasing the arterial oxygen tension, and in part by preventing constriction of capillaries in the coronary circulation. The administration of carbon dioxide in the absence of alkalosis may in some cases delay the recovery period of heart muscle.

NOTE: Since the submission of this paper to the *AMERICAN HEART JOURNAL*, ten additional normal subjects have been tested after inhaling pure oxygen for twenty minutes. In six cases there was an increase in the height of the T wave in two or more leads; in four, there was no change. Of ten additional cases of heart disease, there was an increase in the height of the T wave in one or more leads in six, and in four cases no change was observed.

REFERENCES

1. Rothschild, M. A., and Kissin, M.: Production of the Anginal Syndrome by Induced General Anoxemia, *AM. HEART J.* 8: 729, 1933.
2. Graybiel, A., Missiuro, W., Dill, D. B., and Edwards, H. T.: Experimentally Induced Asphyxiation in Cardiac Patients, *J. Aviation Med.* 8: 178, 1937.
3. Levy, R. L., Barach, A. L., and Bruenn, H. G.: Effects of Induced Oxygen Want in Patients With Cardiac Pain, *AM. HEART J.* 15: 187, 1938.
4. Rothschild, M. A., and Kissin, M.: Induced General Anoxemia Causing S-T Deviation in the Electrocardiogram, *AM. HEART J.* 8: 745, 1933.
5. Katz, L. N., Hamburger, W. W., and Schutz, W. J.: The Effect of Generalized Anoxemia on the Electrocardiogram of Normal Subjects. Its Bearing on the Mechanism of Attacks of Angina Pectoris, *AM. HEART J.* 9: 771, 1934.
6. Levy, R. L., Bruenn, H. G., and Russell, N. G., Jr.: The Use of Electrocardiographic Changes Caused by Induced Anoxemia as a Test for Coronary Insufficiency, *Am. J. M. Sc.* 197: 241, 1939.
7. Rizer, R. I.: Oxygen in the Treatment of Coronary Occlusion, *Minnesota Med.* 12: 506, 1929.
8. Boland, E. W.: Oxygen in High Concentrations for the Relief of Pain, *J. A. M. A.* 114: 1512, 1940.
9. Barach, A. L.: Therapeutic Use of Oxygen in Heart Disease, *Ann. Int. Med.* 5: 428, 1931.
10. Barach, A. L., and Levy, R. L.: Oxygen in Coronary Thrombosis, *J. A. M. A.* 94: 1363, 1930.
11. Barach, A. L., and Steiner, A.: Effect of Inhalation of High Oxygen Concentrations, With and Without Carbon Dioxide, on the Electrocardiogram, *Proc. Soc. Exper. Biol. & Med.* 45: 175, 1940.
12. Van Slyke, D. D., and Neill, J. M.: Determination of Volumes of Gases by Vacuum Extraction and Manometric Measurement, *J. Biol. Chem.* 64: 543, 1924.

13. McDowell, R. J. S.: The Effect of Carbon Dioxide on the Circulation. Part I, *J. Physiol.* 70: 301, 1930.
14. Henderson, Y.: Inhalational Treatment of Angina Pectoris and Intermittent Claudication, *AM. HEART J.* 6: 549, 1931.
15. Hooker, D. R.: Evidence of Functional Activity on the Part of the Capillaries and Venules, *Physiol. Rev.* 1: 137, 1921.
16. Roome, N. W.: The Cardiac Output in Hyperventilation by External Alternating Pressure, *Am. J. Physiol.* 104: 142, 1933.
17. Wolff, H. G., and Lennox, W. G.: Cerebral Circulation; the Effect on Pial Vessels of Variations in the Oxygen and Carbon Dioxide Content of the Blood, *Arch. Neurol. & Psychiat.* 23: 1097, 1930.
18. Lennox, W. G., and Behnke, A. R.: Effect of Increased Oxygen Pressure on the Seizures of Epilepsy, *Arch. Neurol. & Psychiat.* 35: 782, 1936.
19. Lennox, W. G.: Quoted by Lennox, W. G., and Cobb, S.: Epilepsy, *Medicine* 7: 229, 1928.
20. Barker, D. S., Shrader, E. L., and Ronzoni, E.: Effects of Alkalosis and Acidosis Upon the Human Electrocardiogram, *AM. HEART J.* 17: 169, 1939.
21. Kerr, W. J., Dalton, J. W., and Gliebe, P. A.: Some Physical Phenomena Associated With the Anxiety States and Their Relation to Hyperventilation, *Ann. Int. Med.* 11: 961, 1937.
22. Wilson, F. N., Macleod, A. G., and Barker, P. S.: Distribution of Currents of Action and of Injury Displayed by Heart Muscle and Other Excitable Tissues, *Univ. Michigan Studies, Scientific Series No. 10*, 1933.
23. Macleod, A. G.: The Electrogram of Cardiac Muscle, *AM. HEART J.* 15: 165, 1938; *ibid.* 15: 402, 1938. Also, personal communication.
24. Hoff, H. E., and Nahum, L. H.: The Factors Determining the Direction of the T-Wave: The Effect of Heat and Cold Upon the Dextro- and Levocardiogram, *Am. J. Physiol.* 131: 701, 1941.

THE DURATION OF ELECTRICAL SYSTOLE (Q-T INTERVAL) IN CASES OF MASSIVE PERICARDIAL EFFUSION

CHEN-LANG TUNG, M.D.

PEIPING, CHINA

IN CLINICAL practice the differentiation between pericardial effusion and cardiac dilatation is often difficult, and may be impossible.¹⁻³ Pericardial effusion has often been mistaken for cardiac enlargement even after a careful roentgenologic examination, and vice versa. In fact, pericardial paracentesis has not infrequently been attempted in cases of cardiac dilatation; in one such case in this hospital, necropsy revealed no pericardial disease, but, instead, a large tear of the right ventricular wall which had been caused by the exploratory needle. Moreover, pericardial paracentesis has frequently not been done on patients with large pericardial effusions when this procedure was definitely indicated from both diagnostic and therapeutic viewpoints. Such mistakes appear unavoidable in some instances, for the physical and radiologic signs may be alike in the two conditions. In both cases there are often similar cardiac contours, feeble cardiac activity, a small pulse pressure, and congestive heart failure.⁴ Any objective criterion which may aid in differentiating cardiac dilatation with congestive failure from massive pericardial effusion with similar congestive phenomena will have certain theoretical and practical importance.

It occurred to me that, as there is a fundamental difference between the cardiodynamics of congestive heart failure associated with cardiac dilatation and those of pericardial effusion and compression of the heart (cardiac tamponade), such a difference might be reflected in the duration of electrical systole, as measured by the Q-T interval of the electrocardiogram, taking the cardiac rate into consideration. The ordinary type of congestive heart failure is characterized by an outflow stasis. In this condition, although the heart is dilated, and there is an increase in both its systolic and diastolic volume, systole is insufficient and the cardiac output is subnormal.^{5, 6} In the electrocardiogram a relative prolongation of electrical systole at the expense of diastole has been demonstrated.⁷ In congestive failure caused by a large pericardial effusion and compression, the reverse, i.e., an inflow stasis, exists. The heart is compressed by the fluid under tension, so that diastolic relaxation is incomplete. This produces a decrease of both the systolic and diastolic volume of the heart, and results also in a subnormal cardiac output and venous congestion behind the heart.^{4, 8} Ventricular systole is normal as far as ejection is concerned, but is insufficient because the diastolic filling is inadequate. The relative duration of electrical systole in such

From the Department of Medicine, Peiping Union Medical College, Peiping, China.
Received for publication Aug. 11, 1940.

cases has not hitherto been studied, as far as I am aware, but, on theoretical grounds alone, one would expect it to be different from that in cases of myocardial failure. With this in mind the following study was made.

MATERIAL AND METHODS

In order to make this series of cases a simple and homogeneous one, only cases of massive tuberculous pericardial effusion, with signs of cardiac tamponade, such as peripheral venous congestion, hepatomegaly, dependent edema, and, in some cases, ascites, were included. Venous congestion was considered to be moderate when there were engorged cervical veins, an enlarged and tender liver, and slight edema of the legs; it was regarded as pronounced when, in addition, ascites and moderate or marked edema of the legs were present. In most cases there was dyspnea of varying severity. Cases of rheumatic pericarditis and purulent pericarditis were excluded from this study because, in the former, the pericardial effusion is usually too small to have a hydrostatic effect on the heart, and, in the latter, the amount of pus may be small or large, and there is a more extensive complicating subpericardial myocarditis than occurs with tuberculous effusion. Cases of constrictive pericarditis were also excluded because there were only two available for study in which the diagnosis was confirmed at autopsy; furthermore, in this condition the cardiac systole may not be entirely normal.⁹ All patients were observed in the hospital and had careful roentgenologic examinations. Only cases in which the presence of a large pericardial effusion was proved by pericardial paracentesis, or at necropsy, or both, were included in this study. In five cases the diagnosis of a large, tuberculous, pericardial effusion was confirmed at necropsy. In five, tubercle bacilli were recovered from guinea pigs which had been inoculated with pericardial fluid obtained by paracentesis. Pericardial paracentesis was performed on each patient; the number of paracenteses varied from one to sixteen per patient. In all cases large amounts of pericardial fluid (serosanguineous in all but one, which was cloudy) were removed; the amount usually removed was 400 to 800 c.c. In several cases air was injected after the aspiration of fluid, and was found to be in the pericardial cavity on subsequent roentgenologic examinations. The roentgenograms of two patients in this series are reproduced to illustrate the contour of the pericardial sac which was generally observed in the cases reported (Figs. 1-3).

The electrocardiograms were usually taken soon after admission, before any therapeutic measures were carried out. Cases in which digitalis was administered before the record was taken were excluded from this study. Only those electrocardiograms which were taken at a time when the patients were afebrile or had only a subfebrile temperature were included, although the duration of electrical systole was similar in a given case whether or not fever was present. As the amount of fluid withdrawn was usually not maximal, and as electrocardiograms were usually not taken soon after paracentesis, no study was made of any possible change in electrical systole after removal of the fluid. The usual three leads were taken with the patient recumbent or semirecumbent, using the string galvanometer (Hindle). The resistance was always satisfactorily low. The string was standardized so that a current of one millivolt gave a deflection of one centimeter on the film. The study of the electrocardiograms was particularly centered on the amplitude and duration of the QRS and T waves, the Q-T level, the R-R interval and the Q-T interval. The voltage of QRS was considered low when it was less than 5 mm. in the lead showing the greatest amplitude.¹⁰ T waves were regarded as low when they were less than 1 mm. in height. Measurements of the R-R and Q-T intervals of the same four consecutive cycles were made under a magnifying glass, in most cases, in Lead II, and, in some cases, in Lead I or III if T waves were not sharp enough in



Fig. 1.—Case 7, July 11, 1939. Roentgenograph of the chest, showing massive tuberculous pericardial effusion before paracentesis.

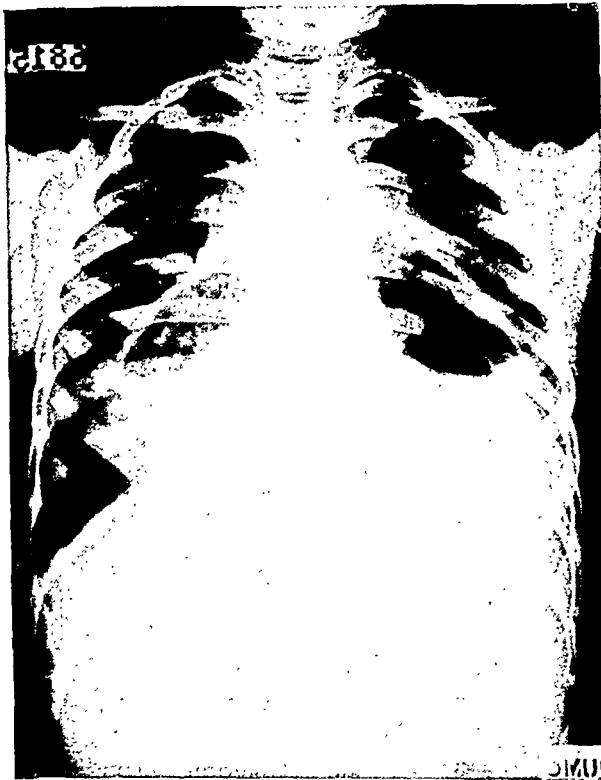


Fig. 2.—Case 7, July 17, 1939. After two pericardial paracenteses. On July 13, 500 c.c. serosanguineous fluid removed. On July 17, 600 c.c. of similar fluid removed and 250 c.c. of air injected. Tubercle bacilli recovered on guinea pig inoculation.

Lead II. The average of the four was taken. Some of the measurements of the Q-T interval were difficult and perhaps inaccurate, although they were probably not far from the figures given in Table I. The "predicted Q-T interval" (Adams) was calculated according to the straight line formulas of Adams for normal males and females.¹¹ The formula for males was:

$$Q-T = 0.1536 R-R + 0.2462 \pm 0.012 \text{ S.E.}$$

That for females was:

$$Q-T = 0.1259 R-R + 0.2789 \pm 0.014 \text{ S.E.}$$

The constant "K" was calculated according to the formula:

$K = Q-T \div \sqrt{R-R}$.¹² The electrocardiograms of some of the patients in this series are reproduced in Figs. 4 to 11.

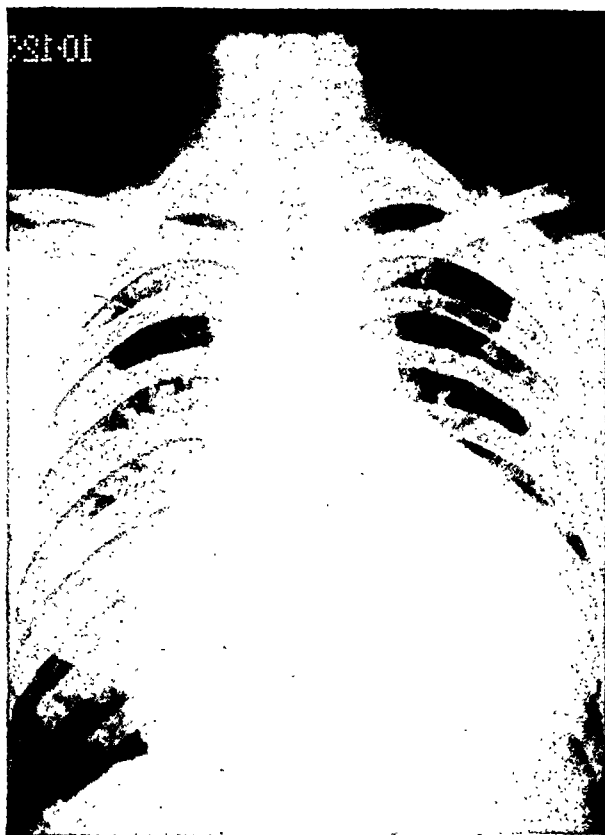


Fig. 3.—Case 10, October 12, 1933. Roentgenograph of the chest, showing massive tuberculous pericardial effusion before paracentesis. Necropsy later confirmed the diagnosis.

RESULTS

The important clinical and electrocardiographic observations are summarized in Table I. It will be seen that, as the systolic arterial pressure tended to be low and as the diastolic remained at about the normal level for Chinese, the pulse pressure was small (mean systolic, 93 mm., mean diastolic, 68 mm., and mean pulse pressure, 25 mm. Hg). The pattern of the electrocardiograms in this series corresponded to what has been noted by others.¹³⁻²⁰ The typical electrocardiogram showed low voltage of QRS, and a low, flat, or inverted T in the standard leads. Low voltage of QRS was not such a constant occurrence as alteration of T deflections,

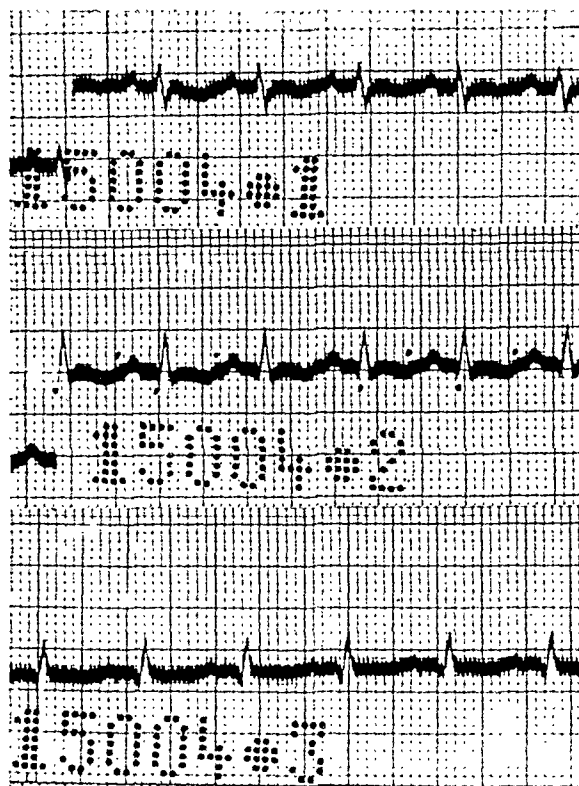


Fig. 4.—Electrocardiogram in Case 1. The Q-T interval is marked with two dots.

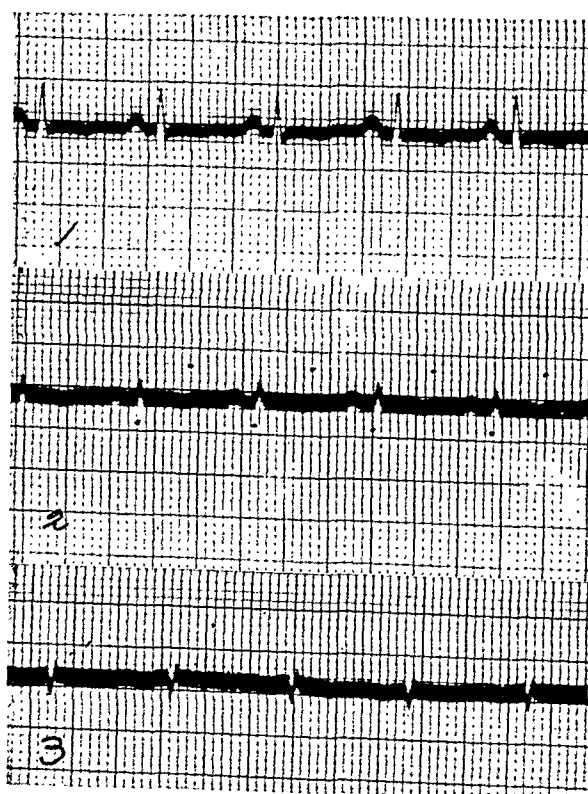


Fig. 5.—Electrocardiogram in Case 2.

TABLE I
CLINICAL AND ELECTROCARDIOGRAPHIC DATA ON FOURTEEN PATIENTS WITH TUBERCULOUS PERICARDIAL EFFUSION

NO.	SEX	AGE (YEARS)	VENOUS CONGESTION	ARTERIAL PRESSURE (MM. HG.)	NO. OF PERICARD. PARA- CENTESES	P-R INTERVAL (SEC.)	R-R INTERVAL (SEC.)	Q-T INTERVAL (SEC.)	PREDICTED Q-T INTERVAL (ADAMS) (SEC.)	DIF- ERENCE (PER CENT)	CON- STANT K*	REMARKS
1	M	32	Marked	90/55	16	0.15	0.460	0.264	0.317	-17	0.389	Low voltage QRS Inverted T all leads
2	M	10	Marked	94/64	3	0.13	0.544	0.254	0.330	-23	0.344	Low voltage QRS Short Q ₃ ; inverted T ₁ , T ₂ ; flat T ₃
3	M	10	Moderate	90/72	1	0.12	0.550	0.322	0.331	-3	0.434	Normal voltage QRS Low R ₁ ; flat T ₃
4	M	38	Moderate	96/80	1(N)	0.13	0.475	0.260	0.319	-18	0.375	Low voltage QRS Low T ₂ ; flat T ₃
5	M	16	Marked	100/78	1	0.16	0.560	0.280(?)	0.322	-16(?)	0.374(?)	Low voltage QRS Low T all leads
6	F	12	Moderate	94/66	2	0.16	0.480	0.253	0.339	-24	0.372	Low voltage QRS Inverted T ₁ , T ₂ Flat T ₃

7	M	8	Moderate	104/68	3(TB)	0.13	0.514	0.306	0.325	- 6	0.427	Low voltage QRS R.A.D. (slight) Low T ₁ ; flat T ₂ Inverted T ₃
8	M	25	Marked	92/78	5(TB)	0.15	0.510	0.290	0.324	-10	0.406	Low voltage QRS Low T all leads
9	M	52	Moderate	80/62	4(N)(TB)	0.16	0.530	0.294	0.328	-10	0.404	Low voltage QRS Low to flat T waves
10	F	14	Marked	74/48	5(N)(TB)	0.16	0.500	0.284	0.342	-17	0.402	Low voltage QRS Inverted T all leads
11	M	24	Marked	90/80	1(N)	0.15	0.556	0.306	0.332	- 8	0.410	Low voltage QRS Inverted T all leads
12	M	24	Moderate	110/70	1	0.16	0.736	0.310	0.359	-14	0.361	Normal voltage QRS Low T all leads Deep Q ₃
13	M	23	Marked	94/74	3(TB)	0.18	0.478	0.276	0.320	-14	0.399	Normal voltage QRS Inverted T ₁ , T ₂
14	F	25	Marked	90/55	3(N)	0.18	0.450	0.272	0.336	-19	0.405	Low R _s , Low T ₁ Inverted T ₂ , T ₃

*K = Q-T interval ÷ $\sqrt{R-R}$ interval.

N, Necropsy; TB, tubercle bacilli recovered on guinea pig inoculation.

Roentgenologic examination showed abnormalities which were typical of massive pericardial effusion in all except Case 4.

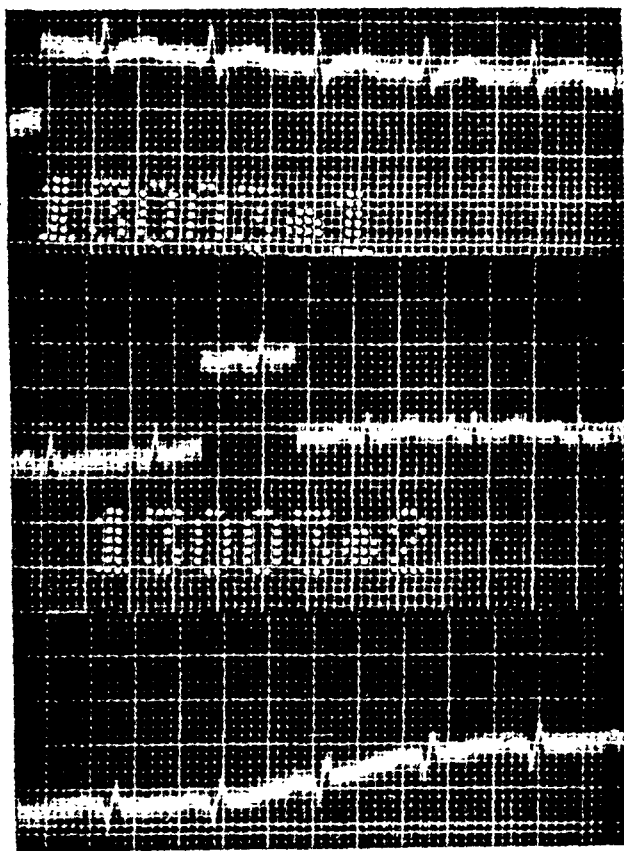


Fig. 6.—Electrocardiogram in Case 4.

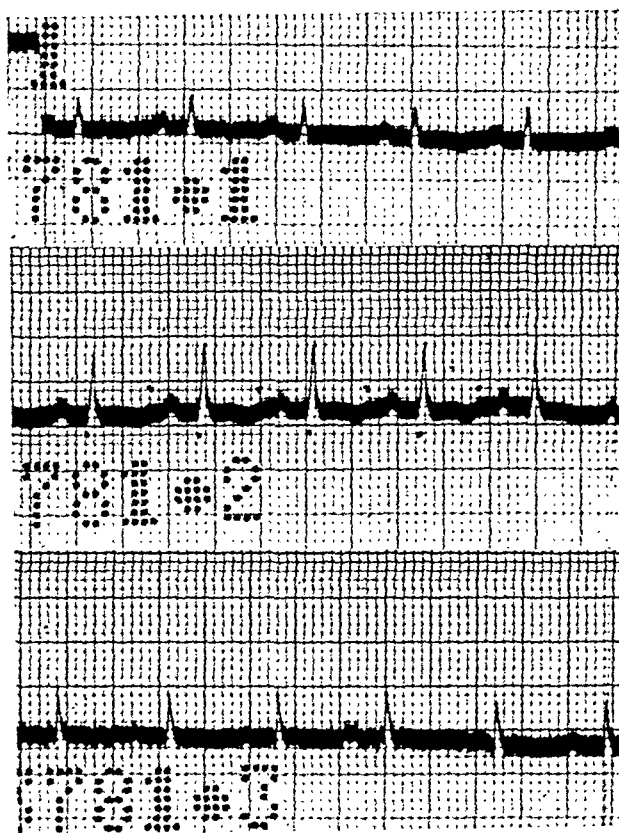


Fig. 7.—Electrocardiogram in Case 6.



Fig. 8.—Electrocardiogram in Case 8.

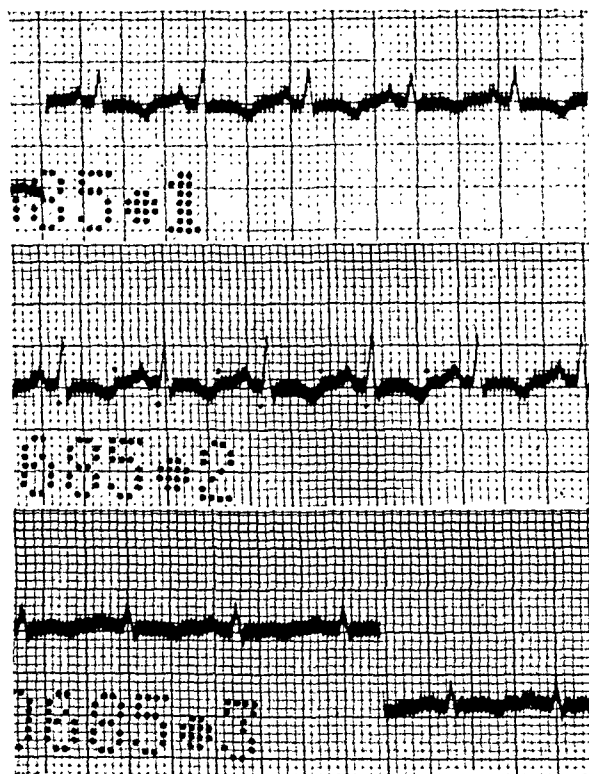


Fig. 9.—Electrocardiogram in Case 10.

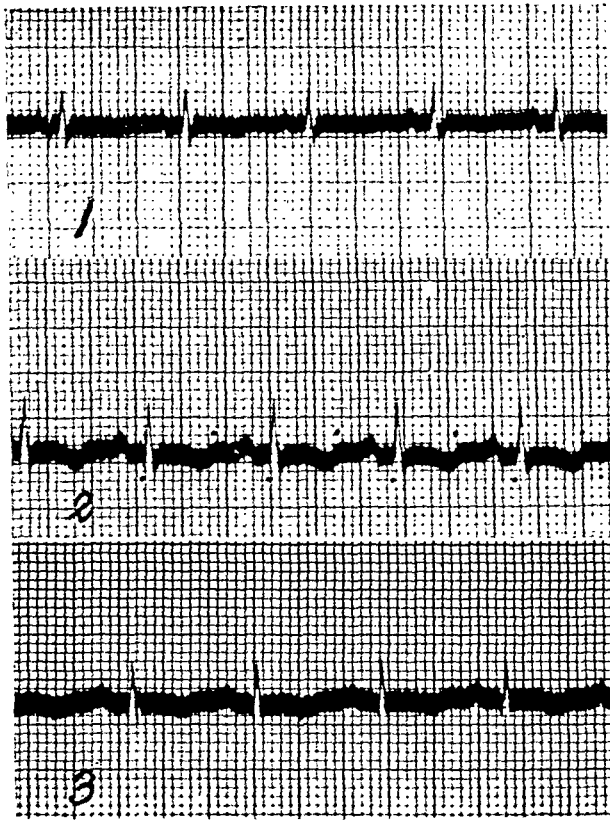


Fig. 10.—Electrocardiogram in Case 11.

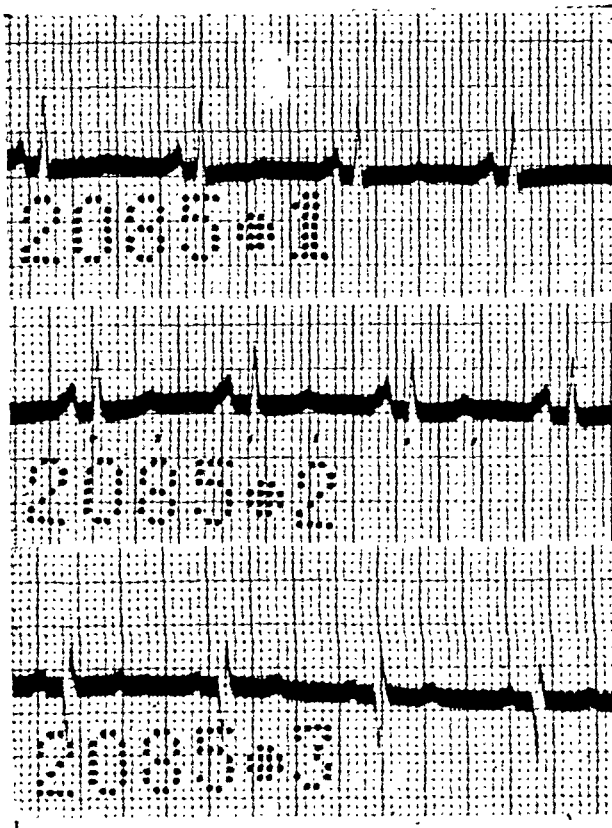


Fig. 11.—Electrocardiogram in Case 12.

for, in three patients with large pericardial effusions (as shown by paracentesis), the voltage of QRS was within the lower limit of normal, whereas in all cases there was definite abnormality of the T deflections. Sinus rhythm was present in all cases, and all but one patient had sinus tachycardia (rate above 100 per minute). The P-R interval was normal.

Special mention may be made of the study of electrical systole, or the Q-T interval, as related to the cycle, or R-R interval. The Q-T interval in each case was shorter than the predicted normal value, calculated according to Adams' formulas (mean difference, 14 per cent). Table I also gives the values of the constant K, calculated from the formula: $K = Q-T \div \sqrt{R-R}$. It will be seen that K varied from 0.344 to 0.434, with a mean value of 0.393 for the twelve male as well as the two female patients. This mean value and its range may be compared with those of the two series of normal subjects reported by Cheer and Li¹² and by Shipley and Hallaran.²¹ Cheer and Li found that the average K was 0.374 in the males and 0.388 in the females, with a range between 0.348 and 0.400 for the former and between 0.355 and 0.421 for the latter. Shipley and Hallaran found that the average K was 0.397 in the males and 0.415 in the females, with a range between 0.337 and 0.433 for the former and between 0.380 and 0.456 for the latter. Thus the mean K and most of the individual values of K in the present series were well within the limits established for normal subjects by these authors. In other words, instead of having a relative prolongation of the Q-T interval, such as that which occurred in patients with congestive heart failure,⁷ this group of patients with pericardial effusion and congestive failure had Q-T intervals which were somewhat shorter than normal when compared with Adams' figures, or about normal when compared with the figures given by Cheer and Li and by Shipley and Hallaran.

In the rather large literature of the electrocardiographic changes in pericardial effusion, no mention has been made as to the effect of such effusion on the Q-T duration. The fact that the duration of electrical systole is normal in patients with massive pericardial effusion which is producing signs of congestive heart failure, if confirmed, may have a theoretical interest as well as a practical value in the clinical differentiation between cardiac dilatation and pericardial effusion.

SUMMARY AND CONCLUSION

An electrocardiographic study was made of a group of fourteen patients with massive, tuberculous, pericardial effusion, the existence of which was confirmed by paracentesis or at necropsy. In all of the patients there were signs of congestive heart failure which was directly attributable to cardiac tamponade (hypodiastolic failure).

The electrocardiographic observation which was of interest in this series of cases was the fact that, taking the heart rate into consideration, the duration of electrical systole (Q-T interval) was normal. This may

aid in the differential diagnosis between marked cardiac dilatation with congestive failure and large pericardial effusion with similar congestive phenomena.

REFERENCES

1. Osler, W., and McCrae, T.: *Modern Medicine*, ed. 3, London, 1927, vol. 4, p. 372, Henry Kimpton.
2. Smith, F. M.: *Internal Medicine* edited by Musser, J. H., ed. 2, Philadelphia, 1934, p. 403-405, Lea & Febiger.
3. Sprague, H. B.: *The Differential Diagnosis of Congestive Heart Failure and Constrictive Pericarditis (Pick's Disease)*, *AM. HEART J.* 12: 443, 1936.
4. Stewart, H. J., Crane, N. F., and Deitrick, J. E.: *Studies of the Circulation in Pericardial Effusion*, *AM. HEART J.* 16: 189, 1938.
5. Altschule, M. D.: *The Pathologic Physiology of Chronic Cardiac Decompensation*, *Medicine* 17: 75, 1938.
6. Fishberg, A. M.: *Heart Failure*, Philadelphia, 1937, Lea & Febiger.
7. Cheer, S. N., and Dieuaide, F. R.: *Studies on the Electrical Systole ("Q-T" Interval) of the Heart. II. Its Duration in Cardiac Failure*, *J. Clin. Investigation* 10: 889, 1931.
8. Beck, C. S.: *Acute and Chronic Compression of the Heart*, *AM. HEART J.* 14: 515, 1937.
9. Stewart, H. J., and Heuer, G. J.: *Chronic Constrictive Pericarditis: Dynamics of the Circulation and Results of Surgical Treatment*, *Arch. Int. Med.* 63: 504, 1939.
10. Bainton, J. H., Levy, R. L., DeGraff, A. C., and Pardee, H. E. B.: *Criteria for the Classification and Diagnosis of Heart Disease*, ed. 3, New York, 1936, New York Tuberculosis and Health Assoc.
11. Adams, W.: *The Normal Duration of the Electrocardiographic Ventricular Complex*, *J. Clin. Investigation* 15: 335, 1936.
12. Cheer, S. N., and Li, R. C.: *Studies on the Electrical Systole ("Q-T" Interval) of the Heart. I. The Duration of Electrical Systole in Normal Chinese*, *Chinese J. Physiol.* 4: 191, 1930.
13. Katz, L. N., Feil, H. S., and Scott, R. W.: *The Electrocardiogram in Pericardial Effusion, Experimental*, *AM. HEART J.* 5: 77, 1929.
14. Scott, R. W., Feil, H. S., and Katz, L. N.: *The Electrocardiogram in Pericardial Effusion, Clinical*, *AM. HEART J.* 5: 68, 1929.
15. Schwab, E. H., and Herrmann, G. R.: *Alterations in the Electrocardiogram in Diseases of the Pericardium*, *Arch. Int. Med.* 55: 917, 1935.
16. Harvey, A. M., and Whitehill, M. R.: *Tuberculous Pericarditis*, *Medicine* 16: 45, 1937.
17. Vander Veer, J. B., and Norris, R. F.: *The Electrocardiographic Changes in Acute Pericarditis: A Clinical and Pathologic Study*, *AM. HEART J.* 14: 31, 1937.
18. Bellet, S., and MacMillan, T. M.: *Electrocardiographic Patterns in Acute Pericarditis*, *Arch. Int. Med.* 61: 381, 1938.
19. Winternitz, M., and Langendorf, R.: *Das Elektrokardiogram der Perikarditis*, *Acta med. Scandinav.* 94: 141, 274, 1938.
20. Noth, P. H., and Barnes, A. R.: *Electrocardiographic Changes Associated With Pericarditis*, *Arch. Int. Med.* 65: 291, 1940.
21. Shipley, R. A., and Hallaran, W. R.: *The Four-Lead Electrocardiogram in Two Hundred Normal Men and Women*, *AM. HEART J.* 11: 325, 1936.

AURICULAR FIBRILLATION IN NORMAL, INTACT ANIMALS AFTER THE INTRAVENOUS INJECTION OF MECHOLYL (ACETYL- β -METHYLCHOLINE)

ARNOLD IGLAUER, M.D., DAVID DAVIS, M.D., AND
MARK D. ALTSCHULE, M.D.
BOSTON, MASS.

AURICULAR fibrillation in man is commonly associated with disease of the heart or the thyroid gland, and the relationship between this arrhythmia and organic disease is emphasized by clinicians. On the other hand, a large number of studies have been made^{1, 2, 3, 4, 5, 6, 7, 8, 9} which show that auricular fibrillation may be produced in normal animals; in many of these, vagal stimulation was an important part of the experimental procedure. Physiologists have therefore stressed the functional origin of the arrhythmia.⁶ The significance of many of these studies is, however, difficult to evaluate, for various anesthetics were used and a good deal of manipulation occurred during the experiments. Accordingly, it was considered desirable to produce auricular fibrillation by means of vagal stimulation in normal, intact, unanesthetized animals. Since the action of mecholyl reproduces the effects of stimulation of the parasympathetic nervous system,¹⁰ this drug was chosen for the study. Although many studies on the action of mecholyl are available, there is no evidence that injection of that substance will cause auricular fibrillation in normal, intact, unanesthetized animals.

MATERIAL AND METHODS

Experiments were performed on dogs and rabbits. In every instance mecholyl* was given intravenously in doses ranging from 0.25 to 2.0 mg. for dogs, and 0.12 and 0.2 mg. for rabbits.

Ten dogs of unascertainable age and breed were used in thirty experiments; their weights ranged between 12.9 and 22.6 kilograms. No anesthesia was employed in most instances; in a few, nembutal intravenously in a dose of 25 to 35 mg. per kilogram, morphine, or ether was used. In thirteen experiments the action of mecholyl alone was studied. In seven others, which were designed to test the effect of anoxia or excess of carbon dioxide on the action of mecholyl, mixtures containing various concentrations of oxygen and carbon dioxide were given from a spirometer by inserting a soft catheter with an inflatable cuff into the trachea of the anesthetized dog. The oxygen concentrations which were used were as low as 3 per cent; the carbon dioxide concentrations varied up to 15 per cent. In one experiment, air enriched with oxygen up to 90 per cent was used. In five experiments mecholyl was given 20 to 90 minutes after the intravenous injection of ouabain in doses of 0.25 and 1.5 mg. In two experiments, five cat units of digalen were given intravenously one hour before mecholyl, and in one other experiment the mecholyl was preceded by 0.5 mg. of prostigmine subcutaneously. In one study mecholyl was given in-

From the Medical Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School, Boston.

Received for publication Aug. 14, 1940.

travenously to a dog which previously had received 1.0 gram of desiccated thyroid U.S.P. daily by mouth for eighteen days. Experiments were done on five rabbits whose weights ranged between 2 and 3 kg. In one dog and one rabbit the vagi were divided in the neck before the injection of mechohyl.

In one dog and two rabbits the heart was observed directly, before, during, and after the period of action of mechohyl; in these animals the chest was opened and positive pressure artificial respiration was used.

In all of the above experiments mechohyl was injected two or more times at intervals of at least ten minutes.

All studies were made by means of a vacuum tube electrocardiograph, using Lead II. Contact electrodes were used for dogs and needle electrodes for rabbits.

OBSERVATIONS

The changed heart rhythms observed in the experiments on dogs were of two general types: (1) auricular fibrillation, and (2) auriculo-ventricular block. Auricular fibrillation occurred at least once in seven of the ten dogs studied, but in one of them only when mechohyl was injected after a toxic dose of ouabain. Fibrillation followed twenty-nine of the sixty-seven injections of 0.5 mg. or more of mechohyl which were given to these seven dogs. Ten injections of 0.5 to 2.0 mg. of mechohyl in the three remaining dogs did not cause fibrillation of the auricles. The initial heart rate in the dogs was 100 to 130 per minute; the first change after the injection of mechohyl was usually a sinus tachycardia, which lasted one to three seconds. When fibrillation supervened it either started immediately after this tachycardia, or was preceded by a few seconds of A-V block (2:1 to 35:1). The onset of auricular fibrillation was usually characterized by a series of coarse auricular waves (Fig. 1), followed by ventricular arrest for two to eight seconds. The ventricular rate immediately after the onset of fibrillation was slow (50 to 80 per minute), and the beating was quite irregular. After fifteen to sixty seconds, however, the beating became less irregular and the rate more rapid, often reaching 300 per minute before reversion to sinus rhythm occurred. When auricular fibrillation was produced the auricular waves were at first very fine and rapid, with a frequency of approximately 1,800 per minute; thirty to ninety seconds later the auricular waves became somewhat coarser and slower. The transition to sinus rhythm was observed in one or two instances, and this occurred without any striking change in ventricular rate. Normal auricular waves appeared suddenly, and the ventricular beating became regular. The duration of the auricular fibrillation which was induced in dogs was usually from one-half to three minutes, but, in one dog, fibrillation persisted for several hours on three separate occasions. In the first instance, the arrhythmia was apparently interrupted after three hours by the injection of 1 mg. of atropine intravenously; in the second, the duration was over eight hours, and, in the third, over three hours.

*The mechohyl used in this study was supplied through the courtesy of Merck and Company, Inc.

When auricular fibrillation did not supervene, auriculoventricular block, with a ratio ranging from 2:1 to 35:1, was the usual response. At the onset of block the auricular rate often became somewhat slower than the control rate, but later often exceeded the control level. When a ventricular response occurred, the auriculoventricular conduction time was not significantly prolonged. The maximal degree of block appeared twenty to thirty seconds after mechohyl was given intravenously. This was followed by lesser grades of block, and, after thirty to ninety seconds, by sinus tachycardia of several minutes' duration.

In occasional instances other arrhythmias were observed, such as sinoauricular block, complete auriculoventricular dissociation, ventricular premature beats, and short periods of ventricular tachycardia. The P waves often became lower after the administration of mechohyl, and changes in the direction of the T waves occurred frequently. Minor alterations in the S-T segment were observed, especially when there were T-wave changes. Even when high-grade A-V block occurred, the duration of the QRS complex was not increased.

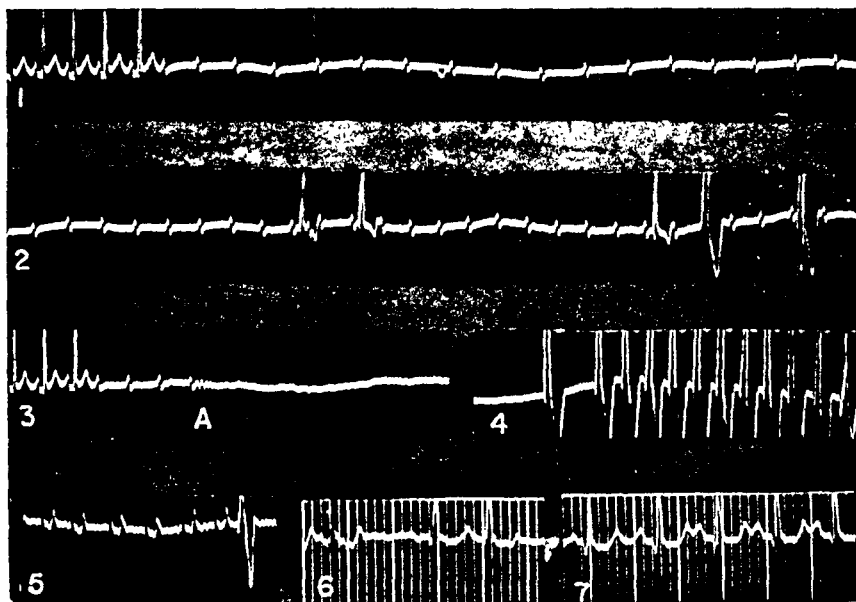


Fig. 1.—1, 2: Continuous tracing from dog, showing transition from sinus rhythm to high grade (26:1) block after injection of 0.75 mg. mechohyl. Note sinus slowing during period of block, and unchanged P-R interval and inverted T wave in conducted beats following block. 3-7: Tracings from another experiment on same dog. "A": onset of auricular fibrillation following short period of A-V block. 4: Twenty seconds later, showing ventricular tachycardia with continued fibrillation of auricles. 5: Thirty seconds later. 6: Twenty seconds later (higher film speed). 7: Thirty seconds later, showing sinus rhythm.

In the dog in which the exposed heart was observed directly after the injection of 0.75 mg. of mechohyl intravenously, the heart stopped beating, and then dilated markedly for a few seconds. Diffuse, fine, fibrillary twitchings of the auricles ensued, followed by the onset of ventricular contractions. The fibrillary twitchings of the auricular wall

could be seen clearly because of the fact that ventricular diastole was long at the onset of fibrillation. The electrocardiogram (Fig. 2) which was taken during this experiment is typical and shows the onset of fibrillation shortly after a complex of sinus origin. After an interval

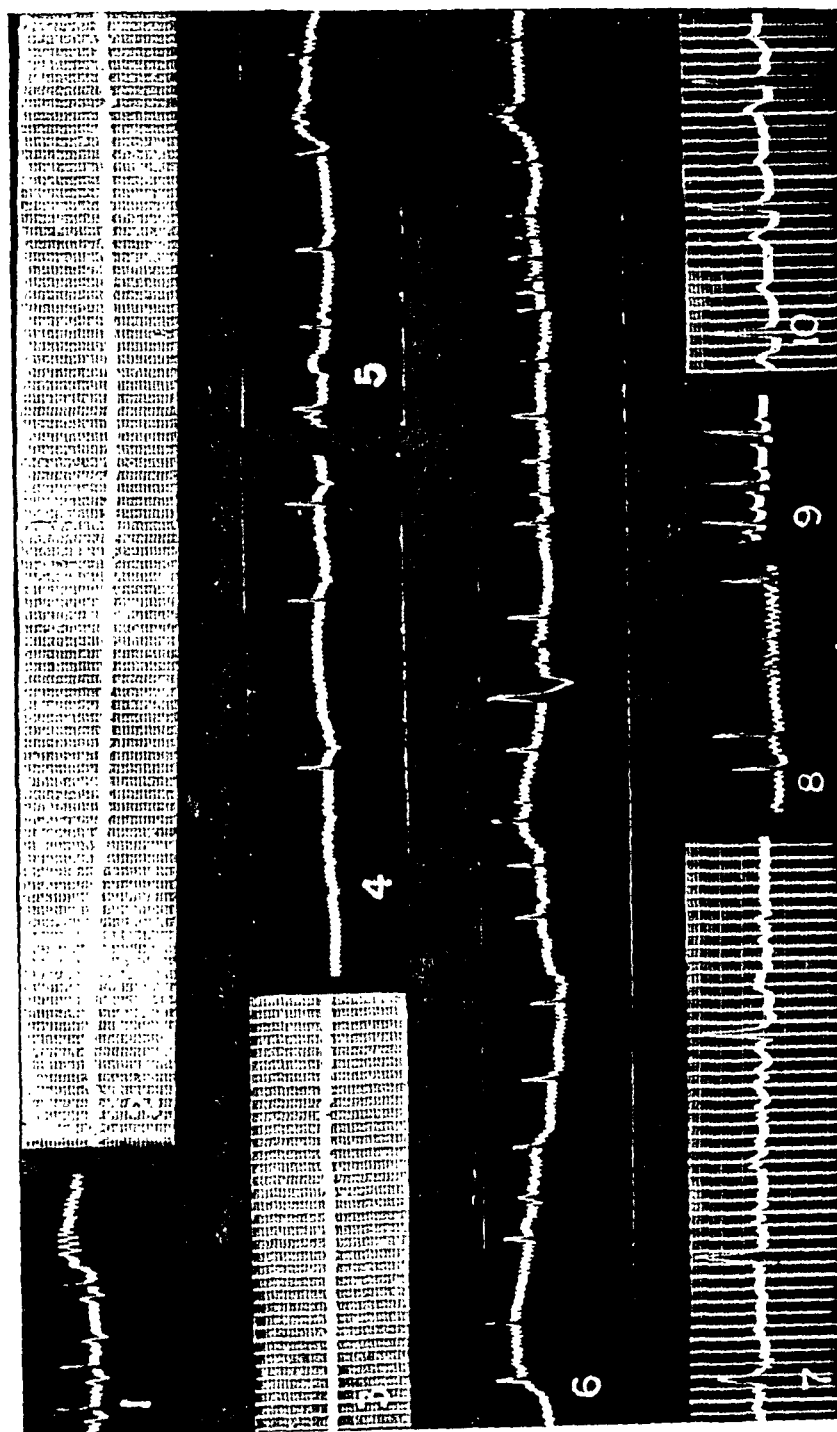


Fig. 2.—Auricular fibrillation observed in 23 kg. dog, with chest exposed, following injection of 0.75 mg. mechohyl (see text, pages 49 and 50). 1: Transition to fibrillation. 2, 3, 4: Consecutive strips showing sequence of events at start of fibrillation (2 and 3 taken at higher film speed). 5: Thirty seconds later. 6: Fifteen seconds after "5." 7 and 8: Consecutive tracings thirty-five seconds later. 9 and 10: Show reversion to sinus rhythm ten seconds later.

of eight seconds, ventricular complexes reappear and gradually increase in rate. Toward the end of the period of fibrillation, the auricular rate decreases from the initial rate of approximately 1800 to 1200 per minute, and the fibrillary waves become coarser.

The effect on the heart of a given injection of mechohyl was unpredictable; the reaction to the same dose in a single experiment varied without apparent reason. It was consequently difficult to evaluate the action of other factors in increasing or decreasing the effect of mechohyl on the heart. However, repeated experiments adequately showed that anoxemia and excess carbon dioxide or oxygen in the ranges used did not alter the activity of mechohyl. Similarly, neither prostigmine nor thyroid, in the dosage used, affected the tendency to fibrillation or the grade of block after the injection of mechohyl. Moderate (0.25 mg.) doses of ouabain did not enhance the action of mechohyl. The action of toxic doses of ouabain was not clear-cut, although 1.5 mg. appeared to facilitate the production of fibrillation in one animal. Fibrillation occurred less frequently in animals under nembutal anesthesia than in unanesthetized animals, but ether did not interfere with the action of mechohyl. Cutting both vagi did not interfere with the production of fibrillation in the dog on which this procedure was carried out.

No dog died as a result of injecting mechohyl intravenously, although tonic convulsions of short duration, apparently associated with ventricular standstill, were noted rather frequently. Profuse salivation occurred regularly after each injection. Urination and defecation occurred infrequently, but passage of flatus was common. An increase in the depth and rate of respiration, sometimes preceded by a short period of apnea, occurred in anesthetized and unanesthetized dogs after the injection of mechohyl. The unanesthetized dogs were restless and seemed uncomfortable shortly after the injection of mechohyl, but recovery from these symptoms was rapid. Prolonged fibrillation in the dog in which it occurred was at a slow rate and without obvious symptoms, and no clinical or electrocardiographic evidence of permanent cardiac change was obtained in any of the experiments on dogs.

The results on rabbits were similar to those on dogs (Fig. 3). Fibrillation occurred in four of the five rabbits which were used, and heart block resembling that noted in dogs also occurred. Fibrillation was induced in one rabbit after cutting the vagi. In two rabbits with chest and pericardium open, fibrillation did not occur spontaneously after large doses (0.12 to 0.2 mg.) of mechohyl, although in one of these animals short periods of auricular fibrillation could be induced by pinching the auricle after the administration of mechohyl. The tracing which was taken at this time resembled those obtained when fibrillation was induced in intact rabbits. In these two animals the heart became markedly dilated after a single injection of mechohyl and did not return to its original size during the period of observation. Several rabbits died, apparently as a result of the injection of mechohyl.

DISCUSSION

There are no available previous reports of the occurrence of auricular fibrillation in normal, intact animals after the injection of mechohyl

intravenously. Cohn and MacLeod¹¹ observed auricular fibrillation in pithed bullfrogs, with open chest, following the administration of mecholyl intravenously, and Nahum and Hoff¹² produced that arrhythmia in dogs by the direct application of mecholyl to the auricles. Mecholyl has been injected intra-arterially in man by several observers^{13, 14} who, however, have not commented on changes in cardiac rhythm. Nahum and Hoff¹⁵ produced auricular fibrillation in patients with thyrotoxicosis by injecting mecholyl subcutaneously.

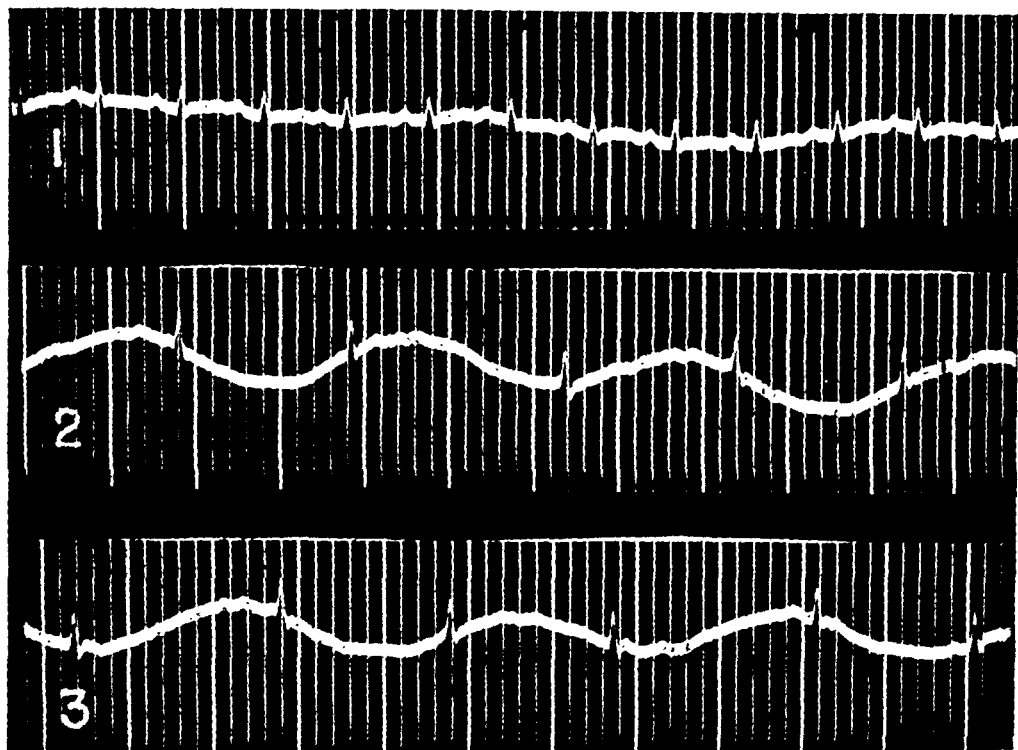


Fig. 3.—Lead II. Auricular fibrillation in rabbit after injection of 0.2 mg. mecholyl intravenously. 1 mv: 1.5 cm.; speed: 3 X normal. 1: Control, showing definite P waves, with regular R-R interval. 2 and 3: Auricular fibrillation, with absent P waves and irregular ventricular beating.

Acetylcholine, a drug which is closely related to mecholyl chemically and pharmacologically, has been shown by Goldenberg and Rothberger⁷ to produce auricular fibrillation in anesthetized, vagotomized dogs when given intravenously. More recently, Noth, et al.,¹⁶ recorded the occurrence of this arrhythmia in one dog which was given acetylcholine. Of great interest and importance are the observations of Battro and Lanari,^{17, 18} who observed auricular fibrillation in three of seventeen normal human subjects after the injection of 40 mg. of acetylcholine into the carotid artery.

The action of various chemical and physical measures in facilitating or inhibiting the experimental production of auricular fibrillation has been studied by several authors. Winterberg² was unable to induce fibrillation by means of electrical stimulation of the vagus during asphyxia, although, after the intravenous administration of digitalis, adrenalin,

muscarine, physostigmine, and calcium salts, vagus stimulation usually produced auricular fibrillation. The results of the present study on oxygen deficiency and carbon dioxide excess corroborate his observation with regard to asphyxia. The possibility that deep nembutal anesthesia inhibits the production of fibrillation by mechohyl is interesting, for phenobarbital inhibits the production of fibrillation by direct electrical stimulation of the heart,⁸ and sodium amytal prevents fibrillation in rabbits after the injection of calcium chloride.²³ The results of Winterberg² and Pines²⁴ suggest that ouabain and prostigmine might increase the tendency to fibrillation, and the clinical observations of Nahum and Hoff²⁵ indicate that thyroid feeding might have the same action. Although these drugs were administered in adequate doses^{25, 26} in our experiments, no striking effect was noted. Since the present experiments deal with a drug which produces locally most of the changes brought on by peripheral stimulation of the vagus, the production of fibrillation by mechohyl in animals with cut vagi is not significant, except to suggest that the action of the drug is not central, but local.

Auricular fibrillation has been produced experimentally in animals by a variety of chemical substances.^{2, 6, 7, 8, 9} Many of these act through the vagus either directly or reflexly, and others have a vagal action in themselves. However, a number of substances with no such action, such as ether, ethyl alcohol, carbon monoxide, arsenic, hydrogen sulfide, and aspirin, have been reported to cause auricular fibrillation in human subjects with normal hearts.²⁷ It appears, therefore, that a variety of chemical agents may cause auricular fibrillation. Nevertheless, the close relationship of mechohyl to acetylcholine, the vagus hormone, cannot be minimized.

Changes in the form of the electrical complex were not analyzed in detail in the present study because only one lead was used and because several reports on the changes produced in the human electrocardiogram by mechohyl are available.^{19, 20} It is of interest, however, that several of the obvious abnormalities in our tracings, i.e., S-A block, A-V block, small P waves, and changes in the T waves, were observed by Einthoven,²¹ in 1908, after electrical stimulation of the vagus nerve in dogs. Our observations on the production of auricular fibrillation in general are also in close agreement with those of other workers who have used other methods to induce this arrhythmia. Almost every available discussion⁶ of the subject comments, either expressly or by implication, on the inexplicable variability in the response to a given stimulus, even in the course of a single experiment. The variability in the duration of the auricular fibrillation, once it has been produced, has also been frequently observed. The occurrence of fine, rapid, auricular waves at the start of the fibrillation, which gradually become coarser, has been noted when direct electrical stimulation of the auricle was the means used to initiate fibrillation.^{1, 22} It has been shown, however, that vagus stimula-

tion when the heart is already fibrillating increases the rate and decreases the amplitude of the auricular waves.^{4, 22} Thus the change in the rate and amplitude of the fibrillary waves which was observed in the present study may have been the result of a progressive decrease in the action of the injected mechohyl.

Physiologists had realized that vagus stimulation produces conditions which are favorable for the production and maintenance of auricular fibrillation, even before the careful study of this problem by Winterberg,¹ in 1907. His observation that faradic stimulation of the vagi facilitated the production of auricular fibrillation by direct electrical stimulation of the auricle, and that vagal stimulation also increased the duration of fibrillation after cessation of local stimulation was confirmed in 1913 by Robinson.⁴ That auricular fibrillation may be produced by vagus stimulation alone has been claimed by several workers.^{3, 4, 5, 28, 29} The earlier experiments were criticized by Winterberg because they dealt with abnormal conditions, as, for instance, a myocardiograph or electrode in contact with the auricle. It is not clear from the protocols of later workers whether or not this source of error has been avoided, but, in any case, the occurrence of auricular fibrillation in normal hearts after vagal stimulation alone must be exceedingly infrequent. Since mechohyl is a synthetic chemical which is not normally present in the body, the results of the present study cannot be interpreted as evidence favoring the possibility that fibrillation may be produced by vagal stimulation alone, although they do re-emphasize the close relationship between that arrhythmia and the vagus nerve. The possible relationship of vagal stimulation to spontaneous auricular fibrillation in man has been suggested by clinical studies,³⁰ as well as by experimental observations.^{15, 17, 18}

SUMMARY AND CONCLUSIONS

1. Auricular fibrillation and heart block were produced in intact and unanesthetized dogs and rabbits by the intravenous injection of mechohyl.

2. Anoxemia, excess carbon dioxide and oxygen, desiccated thyroid, and ouabain did not appear to alter the effect of mechohyl on the cardiac mechanism.

3. The relation of vagal stimulation to auricular fibrillation is discussed.

REFERENCES

1. Winterberg, H.: I. Mitteilung. Über die Wirkung des N. Vagus und accelerans auf das Flimmern des Herzens, *Arch. f. d. ges. Physiol.* 117: 223, 1907.
2. Winterberg, H.: Studien über Herzflimmern. II. Mitteilung. Über die Beeinflussung des Herzflimmerns durch einige Gifte, *Arch. f. d. ges. Physiol.* 122: 361, 1908.
3. Cushny, A. R.: Irregularity of the Heart and Auricular Fibrillation, *Am. J. M. Sc.* 141: 826, 1911.
4. Robinson, G. C.: The Influence of the Vagus Nerves on the Faradized Auricles in the Dog's Heart, *J. Exper. Med.* 17: 429, 1913.
5. Lewis, T., Drury, A. N., and Bulger, H. A.: Observations Upon Flutter and Fibrillation. Part VII. The Effects of Vagus Stimulation, *Heart* 8: 141, 1921.

6. Garrey, W. E.: Auricular Fibrillation, *Physiol. Rev.* 4: 215, 1924.
7. Goldenberg, M., and Rothberger, C. J.: Über die Wirkung von Acetylcholin auf das Warmblüterherz, *Ztschr. f. d. ges. exper. Med.* 94: 151, 1934.
8. Van Dongen, K.: The Action of Some Drugs on Fibrillation of the Heart, *Arch. Internat. de Pharmacodyn. et de Therap.* 53: 80, 1936.
9. Nicholson, W. M., and Soffer, L. J.: Cardiac Arrhythmia in Experimental Suprarenal Insufficiency in Dogs, *Johns Hopkins Hosp. Bull.* 56: 236, 1937.
10. Simonart, A.: On the Action of Certain Derivatives of Choline, *J. Pharmacol. and Exper. Therap.* 46: 157, 1932.
11. Cohn, A. E., and MacLeod, A. G.: The Effect of Acetyl-Beta-Methylcholine on the Frog's Heart, *AM. HEART J.* 17: 305, 1939.
12. Nahum, L. H., and Hoff, H. E.: Production of Auricular Fibrillation by Application of Acetyl-Beta-Methylcholine to Localized Regions on the Auricular Surface, *Proc. Am. Physiol. Soc.*, 52nd annual meeting, 132, 1940.
13. Allen, E. V., and Crisler, G. R.: The Result of Intra-Arterial Injection of Vasodilating Drugs on the Circulation: Observations on Vasomotor Gradient, *J. Clin. Investigation* 16: 649, 1937.
14. Myerson, A., Loman, J., Rinkel, M., and Lesses, M. F.: Human Autonomic Pharmacology. XVIII. Effects of the Intra-Arterial Injection of Acetylcholine, Acetyl-Beta-Methylcholine Chloride, Epinephrine, and Benzedrine Sulfate, *AM. HEART J.* 16: 329, 1938.
15. Nahum, L. H., and Hoff, H. E.: Auricular Fibrillation in Hyperthyroid Patients Produced by Acetyl-B-Methylcholine Chloride, With Observations on the Rôle of the Vagus and Some Exciting Agents in the Genesis of Auricular Fibrillation, *J. A. M. A.* 105: 254, 1935.
16. Noth, P. H., Essex, H. E., and Barnes, A. R.: The Effect of the Intravenous Injection of Acetylcholine on the Electrocardiogram of the Dog, *Proc. Staff Meetings Mayo Clin.* 14: 348, 1939.
17. Battro, A., and Lanari, A.: Inyeccion intracarotidea de acetilcolina en el hombre, *Rev. Soc. argent. de biol.* 12: 171, 1936.
18. Battro, A., and Lanari, A.: Injection intra-carotidienne d'acétylcholine chez l'homme, *Compt. rend. Soc. de biol.* 125: 541, 1937.
19. Page, I. H.: Acetyl-B-Methylcholin (Mecholin). Observations Concerning Its Action on the Blood Pressure, Skin Temperature, and the Heart, as Exhibited by the Electrocardiogram of Hypertensive Patients, *Am. J. M. Sc.* 189: 55, 1935.
20. Dameshek, W., Loman, J., and Myerson, A.: Human Autonomic Pharmacology. VII. The Effect on the Normal Cardiovascular System of Acetyl-Beta-Methylcholine Chloride, Atropine, Prostigmin, Benzedrine, With Especial Reference to the Electrocardiogram, *Am. J. M. Sc.* 195: 88, 1938.
21. Einthoven, W.: Weiteres über das Elektrokardiogramm, *Arch. f. d. ges. Physiol.* 122: 517, 1908.
22. Rothberger, C. J., and Winterberg, H.: Über Vorhofflimmern und Vorhofflattern, *Arch. f. d. ges. Physiol.* 160: 43, 1914.
23. Hoff, H. E., and Nahum, L. H.: An Analysis of the Cardiac Irregularities Produced by Calcium, and Their Prevention by Sodium Amytal, *J. Pharmacol. and Exper. Therap.* 60: 425, 1937.
24. Pines, E.: L'action de l'acétylcholine et du vague sur le coeur après administration de quelques poisons agissant sur le vague cardiaque, *Arch. Internat. de Pharmacodyn. et de Therap.* 49: 91, 1935.
25. Hatcher, R. A.: The Persistence of Action of the Digitalins, *Arch. Int. Med.* 10: 268, 1912.
26. Blalock, A., and Harrison, T. R.: The Effects of Thyroidectomy and Thyroid Feeding on the Cardiac Output. Study Number Four on the Regulation of Circulation, *Surg., Gynec. and Obst.* 44: 617, 1927.
27. Orgain, E. S., Wolff, L., and White, P. D.: Uncomplicated Auricular Fibrillation and Auricular Flutter: Frequent Occurrence and Good Prognosis in Patients Without Other Evidence of Cardiac Disease, *Arch. Int. Med.* 57: 493, 1936.
28. McWilliam, J. A.: On the Phenomena of Inhibition in the Mammalian Heart, *J. Physiol.* 9: 345, 1888.
29. Knoll, P.: Ueber die Wirkung des Herzvagus bei Warmblütern, *Arch. f. d. ges. Physiol.* 67: 587, 1897.
30. Altschule, M. D.: The Relation Between Prolonged P-R Interval and Auricular Fibrillation in Patients With Rheumatic Heart Disease, *AM. HEART J.* 18: 1, 1939.

COR PULMONALE: OBSERVATIONS IN FIFTY AUTOPSY CASES

ROY W. SCOTT, M.D., AND CURTIS F. GARVIN, M.D.
CLEVELAND, OHIO

ONE of the less common etiologic types of heart disease is that which is associated with certain chronic lung affections, notably chronic pulmonary emphysema, and variously called cor pulmonale, emphysema heart, or pulmonary heart disease. Although it is recognized as a distinct entity, there is some difference of opinion regarding its frequency. Particularly conflicting are the present views concerning the role played by chronic lung disease in its etiology.

The common post-mortem occurrence of right ventricular hypertrophy and chronic emphysema, as recorded in past writings, led to the time-honored conception that the narrowing thrombosis and destruction of pulmonary capillaries in emphysema elevated the pulmonary pressure and burdened the right ventricle, which underwent dilatation and hypertrophy and ultimately failed. This explanation of the relation between chronic emphysema and heart disease was accepted by most clinicians and pathologists of a generation ago. Recent observers, however, have questioned the relation of chronic emphysema to right-sided heart failure. White and Bremer,¹ for example, have stated: "A true cor pulmonale (or pulmonary heart disease) is distinctly rare; it is present in certainly not much over 1 per cent of patients with heart disease," and, in the same article, they said: "Ordinarily, asthma, emphysema, and pulmonary tuberculosis, even though of high degree, do not produce cor pulmonale."

From the roentgenologic observations on the heart in eighty cases of chronic emphysema, Parkinson and Hoyle² said: "Cardiac failure from emphysema alone is surprisingly rare," and "Such cardiac signs and symptoms as may appear in emphysema are more likely due to hypertension than to the direct effect of emphysema on the heart."

The most extensive work on the subject of emphysema in the past decade, at least in America, is that of Alexander, Kountz, and their associates, but their conclusions further emphasize the present confusion regarding the relation of emphysema to heart disease, and, particularly, to the so-called cor pulmonale. In one of their earlier articles³ on the effects of long-standing bronchial asthma on the heart, they said: "The impression is gained that, as a rule, the heart remains singularly free from injury after continuous bronchial asthma despite the attendant emphysema," and two years later⁴ they stated: "It is believed that,

From the Department of Medicine of Western Reserve University and the Medical Clinic of Cleveland City Hospital.

Presented in abstract before the Association of American Physicians, Atlantic City, N. J., May 4, 1939.

Received for publication Aug. 31, 1940.

despite peripheral signs which simulate decompensation, advanced emphysema does not necessarily affect the heart." As recently as 1934, in an extensive review of emphysema,⁵ Kountz and Alexander stated: "The preponderance of evidence points to the fact that there is no cardiac lesion in the majority of cases of emphysema." Just two years later⁶ they exactly reversed their opinion and said: "From these observations it appears that the heart is affected in the majority of patients with emphysema." In the light of such contradictory statements on the relation of emphysema to heart disease, further study of the problem seems timely.

The clinical recognition of cor pulmonale before the advent of congestive failure is extremely difficult and often impossible, because symptoms such as dyspnea, orthopnea, and cough are often caused by the accompanying chronic lung disease, and there may be little or no objective evidence implicating the heart. Furthermore, patients with emphysema and other chronic lung affections are usually beyond forty years of age, and, if they are observed during a period of congestive failure, it may be impossible to evaluate the influence of such factors as hypertension and coronary artery disease. Symptoms directly attributable to cor pulmonale appear only after the heart begins to fail, and most of the patients never recover from their first breakdown. It is apparent, therefore, that the clinical recognition of cor pulmonale or the emphysema heart is fraught with much uncertainty, and that conclusions regarding its incidence and the role that chronic lung disease may play in its etiology must depend for their validity upon evidence afforded by post-mortem study.

This paper deals with observations on fifty cases which we believe to be examples of cor pulmonale. They occurred in a series of 6,548 consecutive autopsies which were performed at the Cleveland City Hospital during the past ten years, and constitute 6.3 per cent of 790 autopsied patients who died of heart disease.

CRITERIA FOR THE ANATOMIC DIAGNOSIS OF COR PULMONALE

Examples of right ventricular hypertrophy secondary to mitral valve disease were easily excluded. Realizing that the commonest cause of right ventricular hypertrophy is left ventricular strain, we naturally excluded all cases of aortic valve disease, and those in which there was a significant degree of coronary artery disease. In none of the cases had hypertension been present; furthermore, a careful study of the kidney vessels was made, and no cases in which there was significant renal vascular disease were included.

As we possess no means of measuring the pulmonary blood pressure in man, the only available index of right-sided heart strain is hypertrophy and dilatation of the right ventricle. The thickness of the ventricular wall was used as a criterion of hypertrophy, and only cases in which the right ventricle measured 5 mm. or more were included. This procedure,

of course, does not give information concerning the weight of the right ventricle, because no account is taken of the factor of dilatation. On the other hand, it seems fair to assume that a right ventricle which measures 5 mm. or more is the seat of hypertrophy, and that, by using this criterion, one underestimates rather than overestimates the actual hypertrophy.

Except for two cases in which there was marked compression of the pulmonary artery by an aneurysm at the root of the aorta, all of the patients in this series had advanced lung disease. The incidence and types of lung disease which were observed are shown in Table I.

TABLE I

COR PULMONALE IN RELATION TO LUNG DISEASE IN FORTY-EGHT AUTOPSY CASES

LUNG DISEASE	NO. OF CASES
Chronic emphysema	32
Emphysema with conglomerate silicosis	7
Emphysema with ulcerative tuberculosis	5
Emphysema with fibroid tuberculosis	1
Emphysema with silicotuberculosis	1
Conglomerate silicosis	1
Pulmonary fibrosis	1

In thirty-two cases the lungs showed the changes characteristic of chronic emphysema, together with varying grades of bronchitis, bronchiectasis, and fibrosis. In fourteen instances emphysema was accompanied by ulcerative or fibroid tuberculosis, silicosis, or silicotuberculosis, and, in one case, advanced conglomerate silicosis was the only significant pulmonary lesion. Finally, there was one example of severe bilateral fibrosis of the lungs which was thought, but not proved, to have been caused by syphilis. This case was that of a 29-year-old negress who had a positive blood Wassermann reaction, and had exhibited clinically the cardinal signs and symptoms of right-sided heart failure.

Reference to Table II shows that the heart in the majority of the cases was overweight; in only eleven instances did it weigh less than 400 grams. In twenty-five instances the heart weighed from 400 to 500 grams, and, in fourteen cases, more than 500 grams. No strict correlation between the thickness of the walls of the two ventricles was observed, although, when the right ventricular hypertrophy was extreme, the wall of the left ventricle was thickened in all but one case (W. B., Autopsy No. 9035, in which the walls of both chambers measured 12 mm.).

The degree of right-sided hypertrophy, as indicated by the thickness of the wall of the right ventricle, fell within fairly narrow limits in the majority of cases. For example, in forty-one, or 80 per cent, the right ventricle measured from 5 to 8 mm. In two cases it was 9 mm.; in three, 10 mm.; in one, 11 mm.; in two, 12 mm., and in one, 14 mm. in thickness. Thus, in a few cases, the right ventricular hypertrophy became extreme, but most of the patients succumbed before the right ventricle attained a thickness of more than 8 mm. In two clear examples of in-

creased pulmonary pressure and right-sided heart failure, uncomplicated by lung disease (S.W., Autopsy No. 7102, and H.H., Autopsy No. 11946), in which the pulmonary artery was compressed by an aneurysm at the root of the aorta, the wall of the right ventricle measured 7 mm. in thickness.

Varying grades of left ventricular hypertrophy were observed in the majority of cases; in thirty, or 60 per cent, the left ventricular wall measured 15 mm. in thickness, and in forty-five, or 90 per cent, the left ventricle was 12 mm. or more in thickness. The cause of this rather consistent hypertrophy of the left ventricle is not clear. It could not be ascribed to increased work per se, for every effort was made in this series of cases to exclude factors which burden the left ventricle, i.e., hypertension and aortic valve disease. Neither could it have been the result of coronary disease, for no heart which showed significant changes in the coronary arteries was included in this study. Perhaps the anatomic relation of the two ventricles is such that hypertrophy of one ultimately involves the other. If this be true, it may account, in part, at least, for the frequent occurrence of right ventricular hypertrophy in cases of primary left ventricular strain. For example, hypertrophy of both ventricles is found at autopsy in cases of chronic hypertension in which the patients died of a cerebral accident but never had clinical evidence of left ventricular failure. Obviously, the hypertrophy of the right ventricle in such cases cannot be ascribed to backward failure of the left ventricle.

CLINICAL OBSERVATIONS

The clinical observations in the majority of the cases here recorded were not complete because thirty-five, or 70 per cent, of the patients had advanced congestive failure at the time of admission to the hospital and died within seventy-two hours. The most outstanding features of the clinical course in this group were (1) the relatively short duration and progressive nature of the symptoms of right ventricular failure, and (2) the fact that forty-three, or 86 per cent, died of their first attack of cardiac failure.

Age.—The majority were over 50 years of age. In the group of thirty-two cases in which emphysema was the major lung disease, one patient was 35 years of age, ten were between 40 and 50, 12 were between 50 and 60, and 9 were over 60.

Sex.—All but two of the patients were men.

Place of Birth.—Excluding two cases of pulmonary artery compression from aneurysms and one of extensive pulmonary fibrosis probably caused by syphilis, thirty-two, or 68 per cent, of the patients were foreign born, and most of these were from Southeastern Europe.

We have felt for some time that there was a higher incidence of chronic pulmonary emphysema in the peasant class of Southeastern Europe than in similar classes from other parts of the world, and, in this connection,

TABLE II
CLINICAL AND AUTOPSY DATA IN FIFTY CASES OF COR PULMONALE

NAME	AGE	SEX	COLOR	EKG AXIS DEVIATION	AUTOPSY NO.	LUNGS	HEART WEIGHT GM.	THICKNESS RIGHT VENTRICLE MM.	THICKNESS LEFT VENTRICLE MM.
S.C.	52	M	W	--	6548	Emphysema	400	7	15
A.R.	55,	M	W	--	6852	Emphysema	520	7	15
W.F.	57	M	W	R.A.D.	7080	Emphysema, Ulcerative Tuberculosis	500	8	17
M.O.	60	M	W	--	7304	Emphysema, Conglomerate Silicosis	550	6	15
A.K.	56	M	W	R.A.D.	7365	Emphysema	600	6	15
J.B.	56	M	W	R.A.D.	8039	Emphysema, Bronchiectasis	500	9	20
J.C.	47	M	B	--	8872	Conglomerate Silicosis	350	6	12
W.B.	59	M	B	--	9035	Emphysema, Bronchiectasis	300	12	12
J.H.	49	M	W	--	9043	Emphysema	380	14	18
F.G.	47	M	W	--	9062	Emphysema	500	9	15
A.C.	54	M	W	R.A.D.	9238	Emphysema	350	8	20
A.H.	59	M	W	--	9131	Emphysema	500	10	20
W.G.	67	M	W	--	9195	Emphysema	400	8	17
T.S.	35	M	W	--	9282	Emphysema	500	6	13
N.K.	50	M	W	--	9471	Emphysema	450	8	14
A.B.	48	M	B	--	9709	Emphysema	450	12	20
L.P.	48	M	W	R.A.D.	9803	Emphysema	580	6	15
G.L.	56	M	W	--	10098	Emphysema	350	7	14
M.B.	52	M	W	--	10131	Emphysema, Bronchiectasis	350	5	10
A.D.	58	M	W	--	10142	Emphysema	420	5	11
J.K.	42	M	W	R.A.D.	10321	Emphysema, Ulcerative Tuberculosis	550	5	13
E.M.	45	M	W	--	10510	Emphysema	450	6	19
J.S.	50	M	W	--	10538	Emphysema, Silicotuberculosis	550	5	14

J.M.	40	M.	W	--	10679	Emphysema, Conglomerate Silicosis	500	5	15
O.S.	73	M.	W	--	10904	Emphysema	530	6	13
A.S.	29	F.	B	L.A.D.	11898	Extensive Fibrosis	250	7	17
W.S.	65	M.	W	--	11993	Emphysema, Conglomerate Silicosis	420	8	15
T.O.	62	M.	W	--	11967	Emphysema	400	7	11
W.C.	61	M.	W	R.A.D.	11919	Emphysema, Tuberculosis	420	8	15
S.S.	64	M.	W	--	11996	Emphysema, Bronchiectasis	450	6	12
W.T.	48	M.	W	R.A.D.	12159	Emphysema	720	11	16
J.C.	61	M.	W	--	12161	Emphysema, Conglomerate Silicosis	500	8	20
J.B.	63	M.	W	N.A.D.	12184	Emphysema	420	7	15
A.H.	63	M.	W	L.A.D.	11466	Emphysema, Bronchiectasis	400	6	15
M.E.	43	M.	W	R.A.D.	12329	Emphysema	600	7	18
H.A.	51	M.	W	R.A.D.	11930	Emphysema	400	8	15
F.V.	50	M.	W	R.A.D.	12540	Emphysema	375	8	10
M.S.	52	M.	W	R.A.D.	11978	Emphysema, Bronchiectasis	450	5	13
F.M.	65	M.	W	--	11837	Emphysema	550	10	15
A.Z.	49	F.	W	--	11525	Emphysema	400	6	12
C.M.	52	M.	W	N.A.D.	12574	Emphysema, Conglomerate Silicosis	350	6	12
M.R.	70	M.	W	L.A.D.	12833	Emphysema, Bronchiectasis	675	6	12
J.H.	67	M.	W	--	12878	Emphysema, Conglomerate Silicosis	390	5	14
S.B.	54	M.	W	--	13021	Emphysema, Tuberculosis	530	8	15
W.G.	69	M.	W	--	12918	Emphysema, Tuberculosis	555	5	16
M.V.	52	M.	W	R.A.D.	12925	Emphysema, Conglomerate Silicosis	460	8	10
E.B.	77	M.	W	--	12704	Emphysema	520	7	18
W.T.	45	M.	W	R.A.D.	12176	Bilateral Fibroid Tuberculosis, Emphysema	300	10	15
S.W.	42	M.	B	R.A.D.	7102	Normal	400	7	13
H.H.	60	M.	W	--	11946	Normal	420	7	15

it is interesting that Cleveland has, relative to the total population, a larger number of immigrants from Southeast Europe than eight other large American cities, as shown in Table III. This fact probably has some bearing on the high incidence of cor pulmonale at the Cleveland City Hospital.

TABLE III

PERCENTAGE OF TOTAL POPULATION REPRESENTED BY PERSONS BORN IN SOUTHEAST EUROPE IN NINE UNITED STATES CITIES IN 1930*

CITY	POPULATION	FOREIGN BORN	PERCENTAGE FOREIGN BORN
New York	6,930,446	275,570	3.98
Chicago	3,376,438	116,013	3.44
Philadelphia	1,950,961	30,710	1.57
Detroit	1,568,662	39,941	2.55
Cleveland	900,429	85,540	9.50
Baltimore	804,874	6,058	0.75
Boston	781,188	2,803	0.36
Pittsburgh	669,817	18,706	2.79
Buffalo	573,076	6,028	1.05

*For these data we are indebted to Mr. Howard Whipple Green, Secretary of the Cleveland Public Health Council.

Symptoms and Signs.—Even in those cases in which a reliable history was obtained, it was not always possible to distinguish cardiac symptoms from those caused by the associated pulmonary disease. Cough, dyspnea on exertion, and cyanosis, with some limitation in capacity to exercise, were the usual complaints, and had often continued for several years, whereas the signs of right ventricular failure—venous distention, hepatic enlargement, edema, and ascites—rarely lasted longer than six to eight months. Until the appearance of such signs there was no clear evidence to incriminate the heart. A history of effort angina was obtained in only one instance, and this occurred in a case of syphilitic aortic aneurysm which compressed the pulmonary artery. Four patients had noted substernal pain, and four complained of precordial pain after coughing. Varying grades of dyspnea were observed in every case, and orthopnea was present in all but four patients. Respiratory distress was an outstanding feature, and, unlike that observed in the usual case of left ventricular failure, periodic breathing of the Cheyne-Stokes type and attacks of nocturnal dyspnea (cardiac asthma) were rarely seen. For example, Cheyne-Stokes breathing was observed in two, and nocturnal dyspnea in four, cases.

Cyanosis, like dyspnea and orthopnea, was conspicuous, and often advanced to an extreme grade as the heart failure increased. In all but three cases, distention of the neck veins and hepatic enlargement were noted clinically. Ascites was present in fifteen cases and general anasarca in sixteen. An erythrocyte count was done in thirty-two cases, and in twenty-one of these the cells numbered more than 5,000,000. The highest count observed was 7.9 million, and in this case, before the onset of congestive failure, a diagnosis of polycythemia vera had been made in another hospital. In twenty cases an electrocardiogram was obtained;

it showed right axis deviation in fifteen cases, no deviation in two, and left axis deviation in three cases.

Unfortunately, many patients in this series were so ill at the time of admission and failed so rapidly that satisfactory roentgenologic studies were not possible. In ten out of nineteen cases in which roentgenologic studies were made, the roentgenologist reported enlargement of either the conus pulmonalis or the body of the right ventricle.

SUMMARY

The observations made in this series of cases entirely support the conclusions of older clinicians and pathologists regarding the relation between chronic emphysema and failure of the right side of the heart. The clinical course and autopsy observations indicate that the right ventricle is burdened in emphysema, presumably by an elevation in pulmonary pressure, and that it undergoes dilatation and hypertrophy and ultimately fails. That increased pulmonary pressure burdens the right ventricle and leads ultimately to death from heart failure is shown clearly by two cases in this series in which an aneurysm at the root of the aorta compressed the main pulmonary artery.

In the majority of cases the left ventricle also was hypertrophic, but the cause of this hypertrophy was not apparent. It is suggested that the anatomic relation of the two ventricles is so intimate that hypertrophy of one chamber ultimately involves the other.

REFERENCES

1. White, P. D., and Bremer, O.: Pathological and Clinical Aspects of the Pulmonary Circulation, *New England J. Med.* 209: 1261, 1933.
2. Parkinson, J., and Hoyle, C.: The Heart in Emphysema, *Quart. J. Med.* 6: 59, 1937.
3. Alexander, H. L., Luten, D., and Kountz, W. B.: The Effect on the Heart of Long Standing Bronchial Asthma, *J. A. M. A.* 88: 882, 1927.
4. Kountz, W. B., Alexander, H. L., and Powell, D.: Emphysema Simulating Cardiac Decompensation, *J. A. M. A.* 93: 1369, 1929.
5. Kountz, W. B., and Alexander, H. L.: Emphysema, *Medicine* 13: 251, 1934.
6. Kountz, W. B., Alexander, H. L., and Prinzmetal, M.: The Heart in Emphysema, *AM. HEART J.* 11: 163, 1936.

THE OCCURRENCE IN ANGINA PECTORIS OF ELECTRO-CARDIOGRAPHIC CHANGES SIMILAR IN MAGNITUDE AND IN KIND TO THOSE PRODUCED BY MYOCARDIAL INFARCTION*

FRANK N. WILSON, M.D., AND FRANKLIN D. JOHNSTON, M.D.
ANN ARBOR, MICH.

DURING the last few years we have observed a number of cases of angina pectoris in which electrocardiograms obtained during paroxysms of substernal distress, either spontaneous or induced, have shown striking changes in the form of the ventricular complex comparable in magnitude and similar in kind to those which occur during the first few hours following the sudden occlusion of a large coronary artery. We would like to present here our clinical and electrocardiographic observations in five such cases, and to make a few comments with reference to their interpretation.

CASE 1.—Mr. L. E. T., an American office worker, aged 35 years, was first seen on Feb. 2, 1935. Early in the summer of 1934, while playing golf, he noticed pain on the ulnar side of the left arm which disappeared promptly when he rested. In subsequent attacks the pain began under the middle and upper sternum and radiated to the left arm as its intensity increased. The distress invariably disappeared within two minutes when he stopped exercising. Walking, climbing stairs, and lifting were the types of effort which most frequently caused pain. The symptoms were most likely to develop on exertion in the cold, or on exertion soon after a meal. The pain was severe but dull, and was accompanied by a sensation of fullness. There was no history of rheumatic fever or diphtheria. When he was 17 or 18 years of age, the patient had a penile lesion which was not followed by a skin rash. No anti-syphilitic treatment was administered. In 1917 he had had intestinal obstruction, but recovered without an operation.

On examination there was no enlargement of the heart, but a very faint aortic diastolic murmur was audible along the left border of the sternum when the breath was held after forced expiration. There was slight accentuation of the aortic second sound. The blood pressure was 125/70. The remainder of the physical examination was entirely negative. The Kahn test was strongly positive, and a diagnosis of angina pectoris due to syphilitic aortitis, with obstruction of the coronary orifices, was made.

The electrocardiogram (Fig. 1A) showed slight left axis deviation, not outside normal limits, and a heart rate of 88 per minute. After exertion sufficiently severe to induce mild anginal pain (Fig. 1B) the heart rate was approximately 130 per minute, and the electrocardiogram showed pronounced downward displacement of the RS-T junction in Lead II and less marked RS-T displacement in the same direction in Leads I and III. In Lead I, in which the T wave was originally sharply upright,

From the Department of Internal Medicine, University of Michigan Medical School.

*This study was aided by a grant made to F. N. Wilson by the Horace H. Rackham School of Graduate Studies. It was reported at a meeting of the Association of American Physicians, held on May 31, 1939. See Trans. Assoc. Amer. Phys. 54: 210, 1939.

Received for publication Sept. 1, 1940.

this deflection was flat or slightly inverted. In addition to these changes in the final ventricular deflection, there was a striking increase in the size of the S deflection in Leads II and III.

Nitroglycerine and aminophyllin were prescribed, and the patient reported on Feb. 25 that he was still having attacks, but that they were much less frequent and of shorter duration than formerly. Between Feb. 16, 1935, and April 10, 1935, eight intramuscular injections of bismuth salicylate (2 gr.) were given, and soon after these injections were begun, the patient stated that there was a slight increase in the severity of his symptoms.

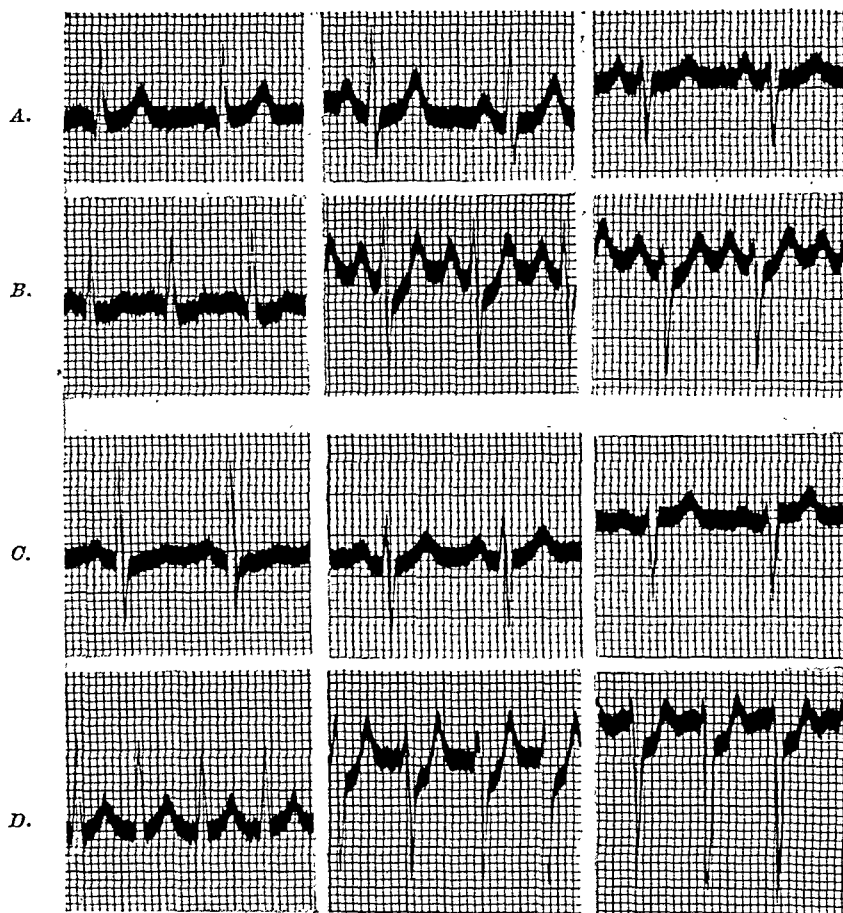


Fig. 1.—A, Case 1. Control electrocardiogram. B, Case 1. Electrocardiogram taken after exertion sufficiently severe to induce mild substernal distress. C, Case 2. Control electrocardiogram. D, Case 2. Electrocardiogram taken during a mild paroxysm of anginal pain induced by exertion. (Reproduced by courtesy of the Macmillan Company.)

On May 14, 1935, the patient's wife reported that he had died on May 4. On this date he went to the assistance of a woman who had fallen and broken her leg. The effort and excitement were promptly followed by a severe attack of chest pain, accompanied by dyspnea. These symptoms persisted until death a few hours later.

CASE 2.—Mr. O. S. G., a gas station attendant, 46 years old, was first seen on Feb. 27, 1928. At that time he was complaining of headache, shortness of breath, giddiness, and a sense of oppression beneath the sternum. He had been having headaches in the occipital region on the right side for eight or nine years, but they had been severe for only two years. The dyspnea, which occurred only on exertion,

and giddiness had been troublesome for one year. The substernal discomfort had occurred on two occasions only and consisted in a burning sensation beneath the surface of the chest. There was a history of gonorrhea many years before, and of three attacks of pneumonia within the preceding nine years.

On examination the heart was borderline in size, and no murmurs were heard. The aortic second sound was somewhat accentuated. The blood pressure was 216/146. The electrocardiogram showed slight left axis deviation. The patient was seen again on Aug. 26, 1929. At this time he stated that after his first visit he did not improve. The basal metabolic rate was measured elsewhere and was reported to have been plus 38 per cent. The administration of iodine and x-ray irradiation of the thyroid gland were followed by improvement, and he was able to return to work. Two weeks before this second visit he began to have attacks of rapid heart action. A tentative diagnosis of paroxysmal tachycardia was made at this time. The blood pressure was 140/80. The basal metabolic rate was -1 per cent.

The patient was seen for the third time on Jan. 15, 1935. He stated that for approximately two years he had felt fairly well, except that during the preceding four or five weeks he had begun to have a burning sensation beneath the upper sternum. This was associated with eructations of gas, but he did not feel distended. This sensation frequently occurred at night. He thought it was often brought on by exertion, but it sometimes lasted for fifteen minutes even if he remained quiet. He could sometimes walk a considerable distance without trouble, but one severe attack was brought on by shoveling snow, and he remained in bed for two days after this. The burning sensation was accompanied by constriction, and radiated to the ulnar side of the left arm.

The heart was not enlarged at this time, either to physical or roentgenologic examination. The aortic second sound was markedly accentuated. No murmurs were heard. The blood pressure was 210/125.

The electrocardiogram (Fig. 1C) which was taken while the patient was at rest showed slight left axis deviation, but was not outside normal limits. The heart rate was approximately 94 per minute. Following exertion sufficiently severe to induce mild substernal distress (Fig. 1D), the heart rate was 180 per minute, and there was pronounced downward displacement of the RS-T junction and segment in Leads II and III of the electrocardiogram. In addition, there were a very conspicuous change in the form of the T deflection in Lead I and a great increase in the size of the S deflections in Leads II and III. The P wave was not distinctly visible, but was apparently superimposed upon the end of the T deflection of the previous cycle because of the rapid heart rate and a slight prolongation of the P-R interval. Extrasystoles were noted after the exercise test, but were not recorded. About one-half hour later, shortly after an orthodiagraphic examination of the heart, the patient was found lying on the floor in one of the dressing rooms of the Department of Roentgenology. He was unconscious, pulseless, and extremely cyanotic, and was making gasping respiratory movements. He could not be revived.

CASE 3.—F. L. K., a physician, aged 66 years, was seen on Dec. 9, 1937. He stated that he had been well until the latter part of October of that year, when he began to have anginal pain. The first attack occurred while he was driving his car, and lasted about fifteen minutes. After this, exertion and excitement frequently induced attacks, and nocturnal attacks often awakened him from sleep. Cold increased the tendency to paroxysms. The pain was felt first in the muscles below and above the elbow joint, was bilateral, and was perhaps more severe on the right side. After it began in the arms, it was felt in the mid-chest on both sides of the sternum, but more on the left. It spread to the neck, jaws, and teeth, and even to the top of the head and as low as the waistline. It consisted in severe aching, with pressure and constriction. The longest attack lasted twenty minutes.

57528

Nitroglycerine gave prompt relief. The first effect of this drug was to cut down the peaks of the waves of pain. The patient did not use tobacco. He said that his blood pressure had been a little high since his student days.

He was distinctly overweight. The heart was not enlarged. There was a faint, late, systolic murmur at the apex. The blood pressure was 160/98. The remainder of the examination was negative.

An electrocardiogram was taken, and this procedure was immediately followed by a spontaneous attack of angina. The first curve (Fig. 2*A*) shows slight left axis deviation, with partially inverted T deflections in Lead I and slight flattening of the RS-T segment in Leads II and III. The electrocardiogram which was taken at the height of the attack (Fig. 2*B*) shows pronounced downward displacement of the RS-T junction and segment and definite changes in the QRS complex, consisting in the development of a prominent S deflection in Lead II and a pronounced increase in the size of the S deflection in Lead III. The heart rate rose from approximately 70 per minute before the attack to approximately 100 per minute when the distress was at its height. In a later and similar spontaneous attack there was a rise in the systolic blood pressure from 160 mm. Hg to 180 mm. Hg. After nitroglycerine the pain subsided promptly (Fig. 2*C*), and the electrocardiogram regained its original form within fifteen minutes (Fig. 2*D*).

The patient died suddenly about one week after these observations were made.

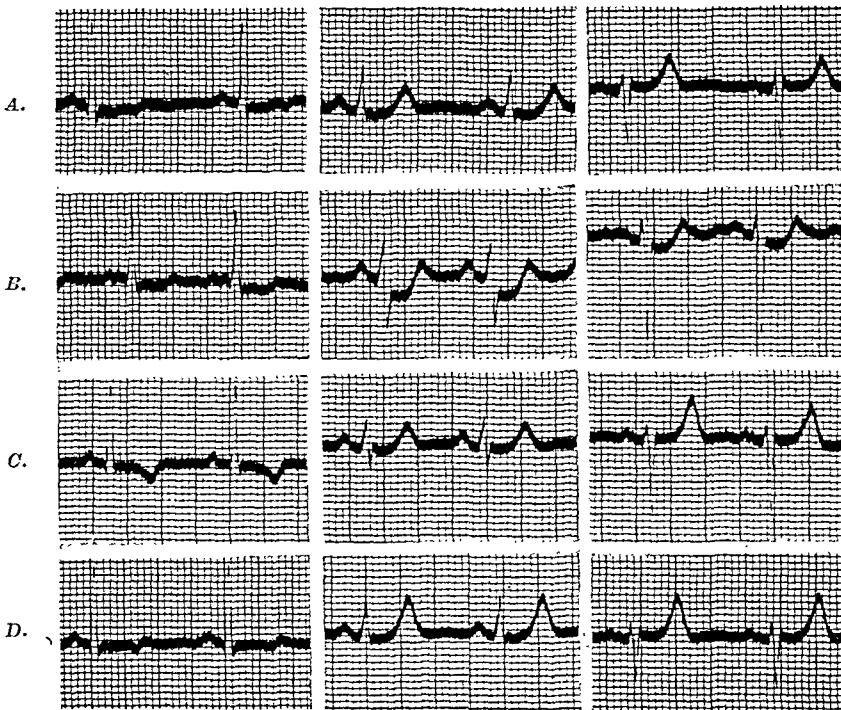


Fig. 2.—Case 3. *A*, Control electrocardiogram. *B*, Taken during a spontaneous attack of anginal pain. *C*, Taken five minutes after *B*, following the administration of nitroglycerine ($\frac{1}{400}$ gr.). *D*, Taken ten minutes after *C*.

CASE 4.—Mr. T. McL., an electrical engineer, was first seen at the University Hospital on June 1, 1927. At this time he was complaining of epigastric pain which occurred two to three hours after meals. This distress was of three years' duration. A clinical diagnosis of peptic ulcer was made, and evidence of duodenal ulcer was discovered on roentgenologic examination. A suitable diet and alkaline powders were prescribed. The patient was not seen again until Dec. 5, 1938, when

he was admitted to the hospital. At this time he was 42 years of age. He stated that the gastric symptoms had eventually disappeared, and that he had been well until November, 1937, when he began to experience sharp, excruciating pain in the precordial region, with radiation to the left arm. These attacks of pain were precipitated at first by heavy lifting, and later by walking. They became more frequent and more severe until May, 1938, when the patient consulted a physician and was put to bed and told to reduce his consumption of tobacco to six or seven cigarettes per day. He had been in the habit of smoking twenty or more cigarettes daily. After he had been in bed for two days, the attacks ceased. He remained in bed for six weeks. After this he gradually increased his activity, and finally returned to work in September, 1938. After he had been working for several weeks, the anginal attacks suddenly returned in severe form, and since that time he had been unable to do anything involving exertion or excitement without distress. He stated that his blood pressure had been elevated for at least three years, but that the systolic pressure had never been above 190.

When he entered the hospital, the patient was having a great many attacks of pain each day, and many attacks at night, as well. Nitroglycerine gave prompt relief, and he was taking 40 to 50 tablets of the drug daily. The pain never lasted more than four or five minutes. It was followed by transient weakness of the left hand.

On examination the patient was slightly obese. The heart was borderline in size. The cardiac rhythm was normal, and no significant murmurs were heard. The heart sounds were loud, and there was slight reduplication of the first sound at the apex. The remainder of the physical examination was entirely negative.

The blood pressure was 165/110. Examination of the blood and urine, kidney function tests, and the Kahn test disclosed nothing abnormal. An orthodiagraphic examination of the heart showed questionable, slight enlargement.

A number of electrocardiograms were taken. All of those which were made when the patient was free of pain showed inversion of the T deflection in Leads II and III and slight downward displacement of the RS-T junction in all three limb leads (Fig. 3).

On the morning of Dec. 10, 1938, the patient was told by his physician to stop smoking. He did so, and had no more attacks of pain until Dec. 14, 1938. On this day he was brought to the Heart Station and was asked to smoke a cigarette. A single chest lead (Lead V_6) was taken before he began to smoke and was repeated at intervals thereafter. The control curve showed flat, inverted T waves and very slight downward RS-T displacement. A typical and severe anginal attack began within a few minutes after the patient started to smoke. It was accompanied by downward RS-T displacement of as much as 0.3 millivolt. The electrocardiographic changes began before the pain and outlasted it. Their exact duration was not ascertained. The heart rate rose during the attack from 77 per minute to 115 per minute. The blood pressure was not taken at this time. Another mild attack of pain occurred without obvious cause in the evening of the day of this experiment. On the following day the patient left the hospital. Further information as to the subsequent course of his illness is rather meager.

On Jan. 16, 1939, the patient's home physician wrote that he was still taking about 20 nitroglycerine tablets per day. He was able to walk from seven to fourteen blocks without pain, but had frequent, severe attacks in the early morning hours, some of which had lasted as long as thirty minutes in spite of nitroglycerin at five-minute intervals.

On Jan. 27, 1939, the patient himself stated that he had continued to have attacks, but that these were less frequent and milder than before, and that he had been able to shovel snow without symptoms.

CASE 5.—V. L., an American attorney, aged 50 years, was admitted to the University Hospital on Feb. 11, 1939. He stated that for the preceding 25 years he had frequently experienced a heavy feeling in the epigastrium, accompanied by pyrosis. These symptoms usually developed in the late afternoon, but sometimes came on fifteen to twenty minutes after a meal. They were promptly relieved by soda, which he was taking 3 or 4 times each day. In May, 1938, he began to have very brief attacks of substernal pressure, accompanied by pain high in the back and in both shoulders, with radiation down the outside of the arms as far as the elbows. These attacks were mild, and he paid little attention to them until late in November, 1938, when he had a severe attack in the evening while he was sitting quietly at home. A second attack occurred the same evening, and thereafter he had attacks daily. In some attacks the pain in the arms was quite severe. Occasionally, there was pain in the left arm only. The distress never lasted more than three or four minutes, and it was never precipitated by excitement or by exertion. Most of the attacks occurred at night and awakened the patient from sleep. For relief he sat up or got out of bed and walked about his room. Nitroglycerine ($\frac{1}{150}$ gr.) relieved the discomfort at once. There was no dyspnea during attacks, but there was a transient feeling of weakness after they subsided. The intensity of the substernal distress and the intensity of the pain in the back and arms seemed to vary independently, and one sensation sometimes occurred without the other.

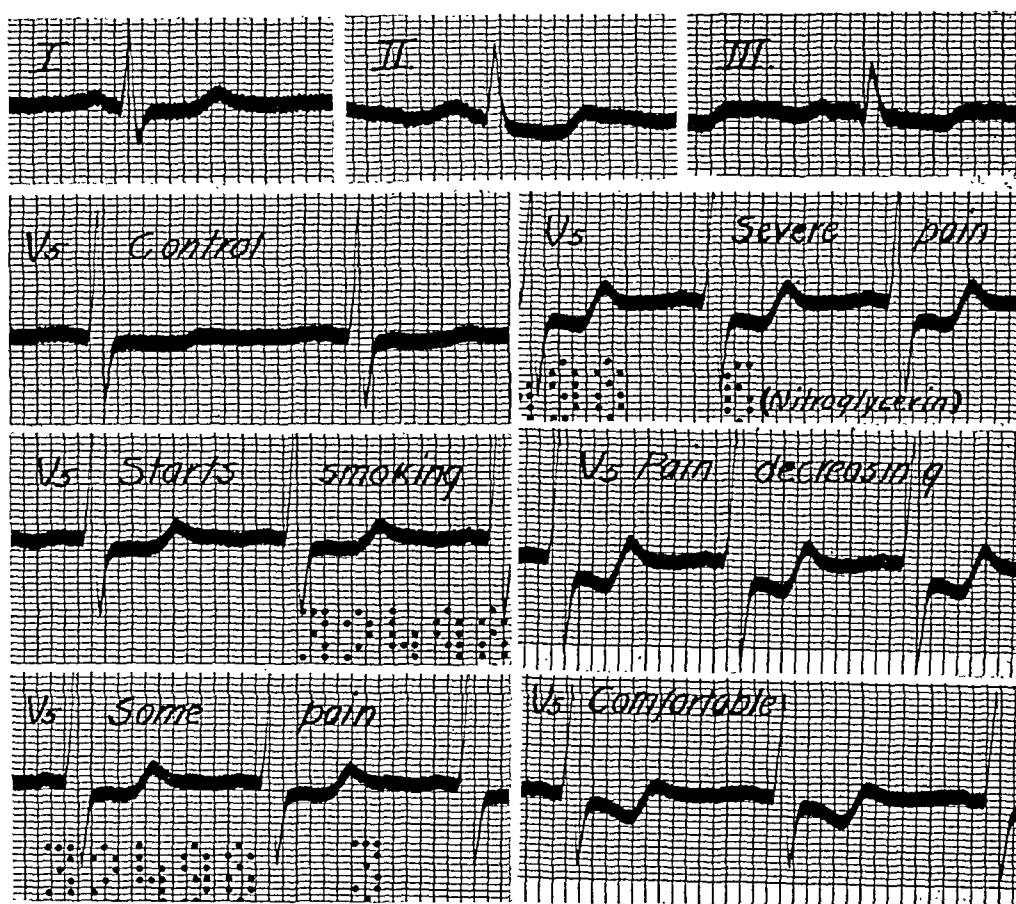


Fig. 3.—Case 4. Top row. Standard electrocardiogram. The remaining curves represent a single precordial lead (V_5), taken before, during, and after an attack of anginal pain induced by smoking and relieved by nitroglycerine.

The past history was negative except for whooping cough, measles, mumps, and chicken pox during childhood, and estivo-autumnal malaria in 1908, and again in

1910. The patient was in the habit of consuming about twenty cigarettes and two or three cups of coffee daily. He used alcohol in moderation.

On physical examination he was moderately obese, but no definite abnormality of any kind was discovered. The blood pressure was 160/100. The Kahn test, gastric analysis, the routine blood cell count, the estimation of the basal metabolic rate, and roentgenologic examination of the cervical spine, the heart and aorta, the gastrointestinal tract, and the gall bladder disclosed no abnormalities. The urine contained a very faint trace of albumin, and a few finely granular casts were found in the sediment. A number of electrocardiograms were taken while the patient was at rest, and one after mild exertion. All of these curves were considered well within normal limits. One of these electrocardiograms, taken on Feb. 11, 1939, is reproduced in Figure 4*A*.

While in the hospital the patient continued to have two or three of his attacks daily. Most of these attacks occurred between 7 P.M. and 8 A.M. Aminophyllin (0.2 Gm. q.i.d.) was given without noticeable effect upon the frequency of the attacks. On one occasion the blood pressure was taken during an attack and was found to be 200/120. There was a daily rise in temperature to 99° or 99.5° F.

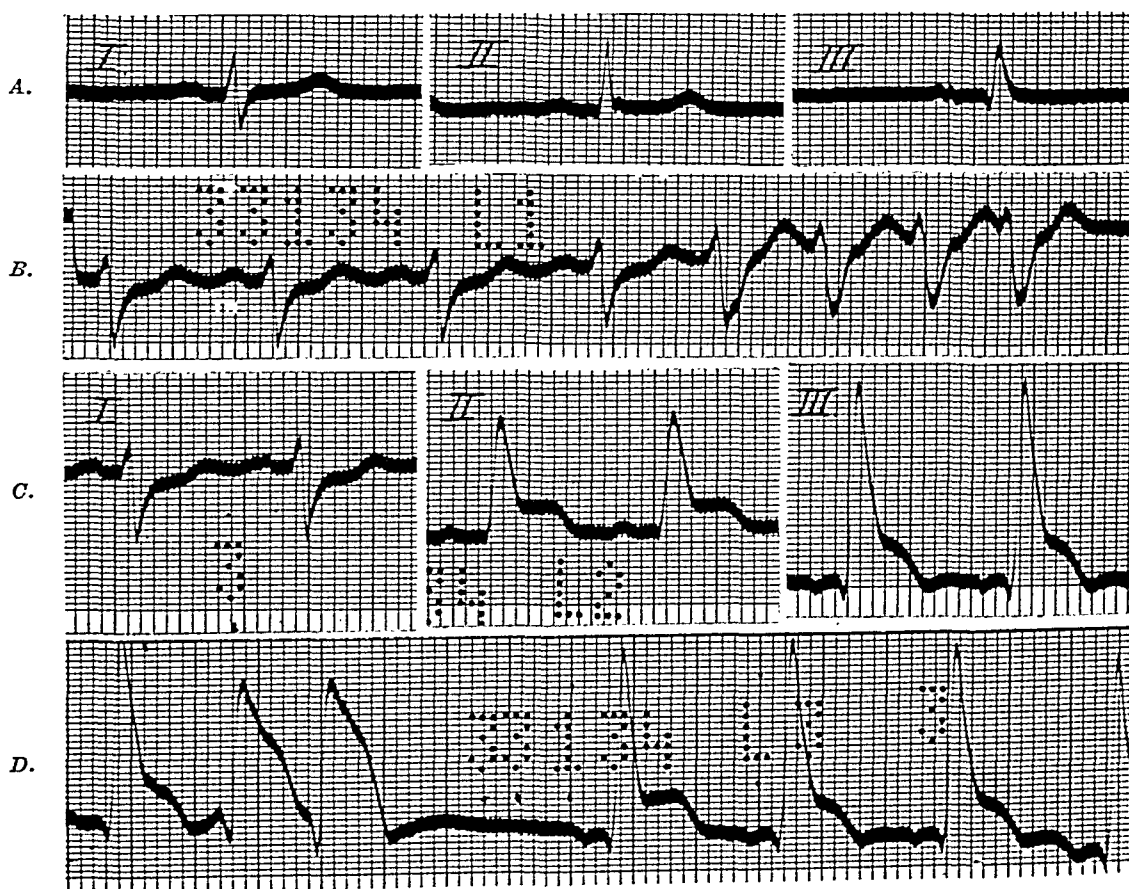


Fig. 4.—Case 5. *A*, Standard electrocardiogram. *B*, Lead I taken during the early stages of a spontaneous attack of anginal pain. *C*, Standard electrocardiogram taken at the height of the attack. *D*, Lead III, showing ventricular extrasystoles of monophasic outline.

On Feb. 18, 1939, a series of electrocardiograms was taken during a severe attack. The earliest curves of this series (Fig. 4*B*) show single ventricular extrasystoles and runs of ventricular extrasystoles constituting very brief paroxysms of ventricular tachycardia. In all of the electrocardiograms which were taken at the height of the distress (Fig. 4*C* and 4*D*), the QRS interval measures approximately 0.16 second, the chief initial deflection (*R*) is greatly increased in height in Leads II

and III, and the RS-T junction is greatly displaced from the isoelectric level. The RS-T displacement is downward in Lead I and upward in Leads II and III and resembles that seen in the early stages of infarction of the diaphragmatic wall of the heart. The extrasystolic ventricular complexes became practically monophasic as a result of the magnitude of this displacement of the junction of the initial and final deflections.

Following the administration of nitroglycerine the patient's distress disappeared promptly, and within a few minutes the electrocardiogram had practically regained its normal outline.

The patient was discharged from the hospital on Feb. 18, 1939, but was asked to return on Feb. 21, 1939, in order that further electrocardiographic studies might be carried out. A control electrocardiogram taken at 11:42 A.M. on this date shows no abnormalities (Fig. 5A). The heart rate at this time was 86 per minute, and the blood pressure was 138/88. The patient was then asked to smoke two cigarettes. When he had finished smoking, at 12:10 P.M., he complained of a slight burning sensation on the lateral aspect of the left upper arm; the heart rate was 94 per minute and the blood pressure was 140/88. The electrocardiogram (Fig. 5B) showed slight downward displacement of the RS-T junction in Lead I and pronounced upward displacement of this junction in Leads II and III. At 12:20 P.M. the electrocardiogram had returned to normal; the heart rate was 90 per minute and the blood pressure was exactly the same as at 12:10 P.M.

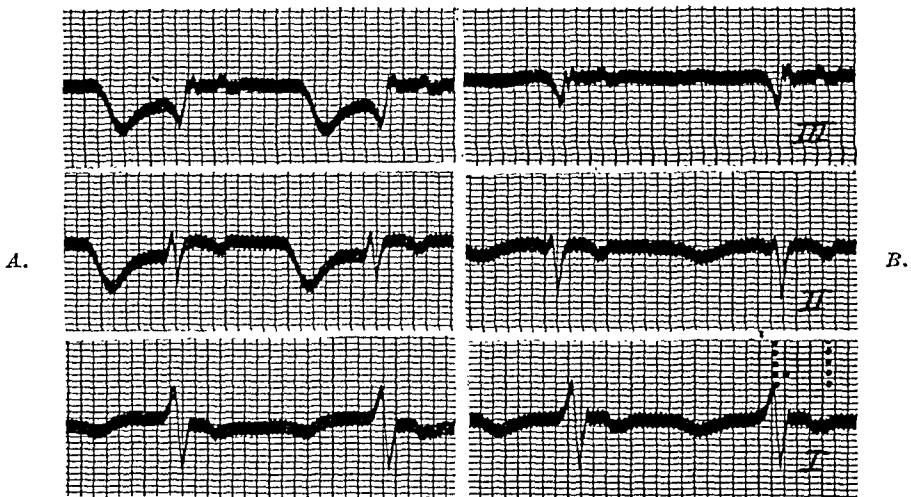


Fig. 5.—Case 5. A, Standard electrocardiogram before smoking. B, Standard electrocardiogram a few minutes after smoking two cigarettes.

A heavy luncheon had no effect upon the form of the electrocardiogram which was taken at 1:03 P.M., when the heart rate was 100 and the blood pressure 183/80. In the course of the afternoon it was observed that the electrocardiograms which were taken shortly after the patient had finished a cigarette did not always show RS-T displacement. He was then connected to a cathode-ray electrocardiograph so that the electrocardiogram might be observed continuously as a standing wave on the screen of the cathode-ray tube. It was then found that, while he was smoking, pronounced RS-T displacement came and went at frequent intervals. On each occasion it lasted fifteen to twenty seconds only. When he had finished smoking it soon disappeared permanently.

Because of these observations the patient was asked to discontinue smoking. Aminophyllin, erythrol tetranitrate, and quinidine, and a reduction diet were prescribed. He has continued to have attacks, but they have been less frequent and less severe. A study of his sensitivity to foreign proteins is being carried out.

DISCUSSION

The electrocardiographic changes which occurred during a spontaneous attack of anginal pain in Case 3 and those which occurred following exertion sufficiently severe to induce mild pain in Cases 1 and 2 are strikingly similar. In all three instances there was a pronounced increase in the size of the S deflection in Leads II and III and pronounced downward RS-T displacement in Leads II and III. Changes of this kind in the QRS complex have not, so far as we know, been observed in coronary occlusion. The RS-T displacement, however, is similar in magnitude and in kind to that seen immediately following sudden occlusion of the anterior descending branch of the left coronary artery. There is one difference. Following occlusion of the artery mentioned the RS-T displacement is usually definitely discordant, i.e., it is upward in Lead I and downward in Lead III. In the three cases of angina pectoris described, however, the RS-T displacement is either concordant (downward in all three leads) or so inconspicuous in Lead I as to make its classification as concordant or discordant difficult.

Electrocardiographic changes of the same kind, but even greater in magnitude, so far as the RS-T displacement is concerned, were recorded under similar circumstances by Scherf.¹

The electrocardiographic changes which occurred during a spontaneous attack of anginal pain in Case 5 are of a different kind. Here the RS-T displacement is definitely discordant (downward in Lead I and upward in Leads II and III) and not distinguishable in type or in magnitude from that frequently seen immediately following infarction of the posterior or diaphragmatic wall of the heart. The changes in the QRS complex are striking, but difficult to classify. The great increase in the QRS interval indicates that a pronounced disturbance in intraventricular conduction occurred, but whether this was dependent upon the development of block in the right branch of the His bundle or upon a widespread depression of the specialized ventricular tissues is not clear. It should be noted that prominent Q deflections in Leads II and III, such as are commonly seen following infarction of the posterior wall of the heart, did not appear. Brow and Holman² recorded transient RS-T displacement of large magnitude and of this same type during a spontaneous attack of anginal pain. In that instance, however, there was a deepening of the Q deflection in Lead II immediately after the attack, and an electrocardiogram which was taken four months later strongly suggests that there was an infarct in the posterior wall of the heart at that time. As to when this infarction occurred the history gave no unequivocal clue.

The electrocardiographic changes which occurred in Case 4 during an anginal attack induced by smoking were recorded in Lead V₆ only. The

RS-T displacement is similar in magnitude and in kind to that seen in the early stages of infarction of the posterior wall of the heart, but no QRS changes are present.

The electrocardiographic changes described are similar in magnitude and in duration to those produced in animal experiments by temporary occlusion of one of the large coronary arteries. They indicate that the disturbances in the coronary circulation which occur during paroxysms of anginal pain are sometimes of very great magnitude. It is not surprising that sudden death, presumably from ventricular fibrillation, is a not uncommon event in angina pectoris, even when this condition is not complicated by coronary thrombosis.

It seems to be the prevailing opinion that the substernal discomfort and transient electrocardiographic changes which occur in anginal paroxysms are dependent upon myocardial ischemia brought about by an increase in the work of the heart, rather than by a change in the caliber of the coronary arteries affected. When, as in Case 5, pronounced electrocardiographic changes of the kind produced by temporary occlusion of a large coronary artery appear, disappear, and reappear without any material increase in heart rate or in blood pressure, this view is clearly untenable. It must, we think, be admitted that in some instances anginal paroxysms are precipitated by contraction of the coronary arteries involved. Whether contraction of the larger coronary arteries takes place, or whether it is the caliber of the arterioles that changes, it is not possible to say. The character of the electrocardiographic changes suggests that the change in arterial or arteriolar caliber is local, not general. The electrocardiographic changes which are attributed to myocardial ischemia and the subjective changes seem to vary independently both in magnitude and duration. This circumstance, together with the evidence that coronary spasm does sometimes cause anginal paroxysms, makes it seem possible that the stimuli which gave rise to the subjective sensations are of arterial rather than of myocardial origin.

The lack of parallelism between the magnitude of the electrocardiographic changes, and hence we may assume of the disturbances of the coronary circulation, and the work of the heart, as represented by the increase in heart rate, in blood pressure, or in both, was not, in our judgment, confined to Case 5, but also existed in Case 3 and probably in Case 4.

It has been clearly demonstrated that cigarette smoking produces constriction of the peripheral arterioles, both in healthy subjects³ and in patients with angina pectoris.⁴ Healthy young subjects may also display electrocardiographic changes immediately after smoking.^{5, 6} Cases have frequently been reported in which precordial pain, not definitely anginal in character, was induced by smoking and disappeared promptly when this habit was given up. A few instances of this kind have come

to the personal attention of the authors. Instances have also been reported in which a patient subject to typical anginal paroxysms could induce an attack by smoking.⁴ Cases 4 and 5 apparently belong in this category. It is our opinion that in both of these cases some part of the coronary arterial system was the seat of a disease process, presumably atherosclerotic in nature, and that the affected vessels were abnormally sensitive to nicotine or to some other constituent of cigarette smoke. The observations made in Case 5 strongly support this view. They do not, perhaps, establish it as correct beyond question.

SUMMARY

The pronounced electrocardiographic changes which sometimes occur during a paroxysm of angina pectoris indicate that the disturbance of the coronary circulation which occurs in this condition is at times as great as that produced by the sudden occlusion of a large coronary artery.

Attacks of anginal pain may occur which are accompanied by profound alterations of the electrocardiogram under circumstances which make it necessary to assume that the attendant myocardial ischemia is due to a change in the caliber of the coronary arteries affected, rather than to an increase in the work of the heart alone.

Nicotine or some other constituent of cigarette smoke sometimes induces coronary "spasm" in patients who are subject to angina pectoris.

REFERENCES

1. Scherf, D.: Koronarerkrankungen, *Ergeb. d. ges. Med.* 20: 237, 1935.
2. Brow, G. R., and Holman, D. V.: Electrocardiographic Study During a Paroxysm of Angina Pectoris, *AM. HEART J.* 9: 259, 1933.
3. Maddock, W. G., and Coller, F. A.: Peripheral Vasoconstriction by Tobacco and Its Relation to Thrombo-Angiitis Obliterans, *Ann. Surg.* 98: 70, 1933.
4. Ralli, E. P., and Oppenheimer, B. S.: Changes in the Peripheral Circulation Accompanying "Tobacco Angina," *Proc. Soc. Exper. Biol. and Med.* 26: 9, 1928.
5. Segal, H. L.: Cigarette Smoking: I. As a Cause of Fatigue. II. Effect on the Electrocardiogram With and Without the Use of Filters, *Am. J. M. Sc.* 196: 851, 1938.
6. Graybiel, A., Starr, R. S., and White, P. D.: Electrocardiographic Changes Following the Inhalation of Tobacco Smoke, *AM. HEART J.* 15: 89, 1938.

LUMBAR SYMPATHECTOMY IN THE TREATMENT OF SELECTED CASES OF PERIPHERAL ARTERIOSCLEROTIC DISEASE

LAWRENCE N. ATLAS, M.D.
CLEVELAND, OHIO

IT IS generally agreed that a therapeutic increase in the volume of blood flow through ischemic tissue is dependent on methods which are capable of producing a dilatation of the small vessel bed in the ischemic part. It has also been established that a collateral arterial network will hypertrophy in response to an increase in the volume of flow through it; and that, for practical therapeutic purposes, such an increase is also dependent on a diminution in the peripheral resistance to blood flow, as brought about by dilatation of the small vessel bed into which that collateral network ultimately empties. If sympathetic vasoconstrictor impulses should inhibit the therapeutic relaxation of the arteriolar bed, or render such relaxation ephemeral, then conservative vasodilating therapy will neither relieve the ischemic condition nor increase the potential vascular reserve through hypertrophy of a collateral arterial network. It has been observed that sympathetic vasoconstrictor tone constitutes such a barrier to medical treatment in a significant number of instances of arteriosclerotic disease of the lower extremity. The following is a case in point. It illustrates what may be the eventual outcome when sympathetic vasoconstrictor tone is not removed surgically.

CASE 60141.—M. D., a 61-year-old white man, was first seen on Aug. 21, 1937. During the previous year he had suffered from intermittent claudication, with pain and severe subjective coldness of his right foot. Examination showed that there was no palpable pulsation in the right dorsalis pedis or posterior tibial artery. Oscillometry revealed a trace of pulsation at the level of the lower leg. There was some pallor of the right foot on elevation, but no rubor or cyanosis, and the nutritional status was good. The foot was cold to the touch, but, following a procaine block of the right lumbar sympathetic trunk, it became palpably warm, and the skin temperatures of the toes rose from 24.5° C. to a vasodilatation level of 29.5° C. (Fig. 1). The patient was given a course of conservative treatments consisting of intravenous injections of hypertonic saline, short-wave diathermy, and treatment with the intermittent venous occlusion cuff twice a week. At home he took daily, warm, leg baths, Buerger's exercises, and whiskey. He was given detailed instructions on the care of his feet. Three months of this treatment gave no relief. A Landis test was then done to ascertain whether conservative vasodilating treatment was actually capable of relaxing the small vessel bed in the foot. The patient's arms were immersed in water at 120° F., and his body was wrapped in blankets. At the end of forty minutes the test had to be discontinued because it was too enervating. No rise occurred in the skin temperatures of the toes in this forty-minute period (Fig. 2).

From the Peripheral Vascular Clinic, Department of Surgery, Cleveland City Hospital, and from the Department of Surgery, School of Medicine, Western Reserve University.

Received for publication Sept. 5, 1940.

Therefore, it was felt that conservative vasodilating therapy could not possibly be effective in the face of such persistent sympathetic vasoconstrictor tone, and a lumbar sympathectomy was advised. However, the patient had a dread of any operative interference, and he refused. This patient was followed for a period of almost three years, and during this time he received intensive, conservative, vasodilating therapy; but his condition, both subjectively and objectively, grew slowly worse. Two years from the time he was first seen, advanced color changes, with atrophy of the skin and subcutaneous tissue of the foot, appeared. The pain was very severe. The condition progressed to massive gangrene of the foot, and, in June, 1940, the foot was amputated.

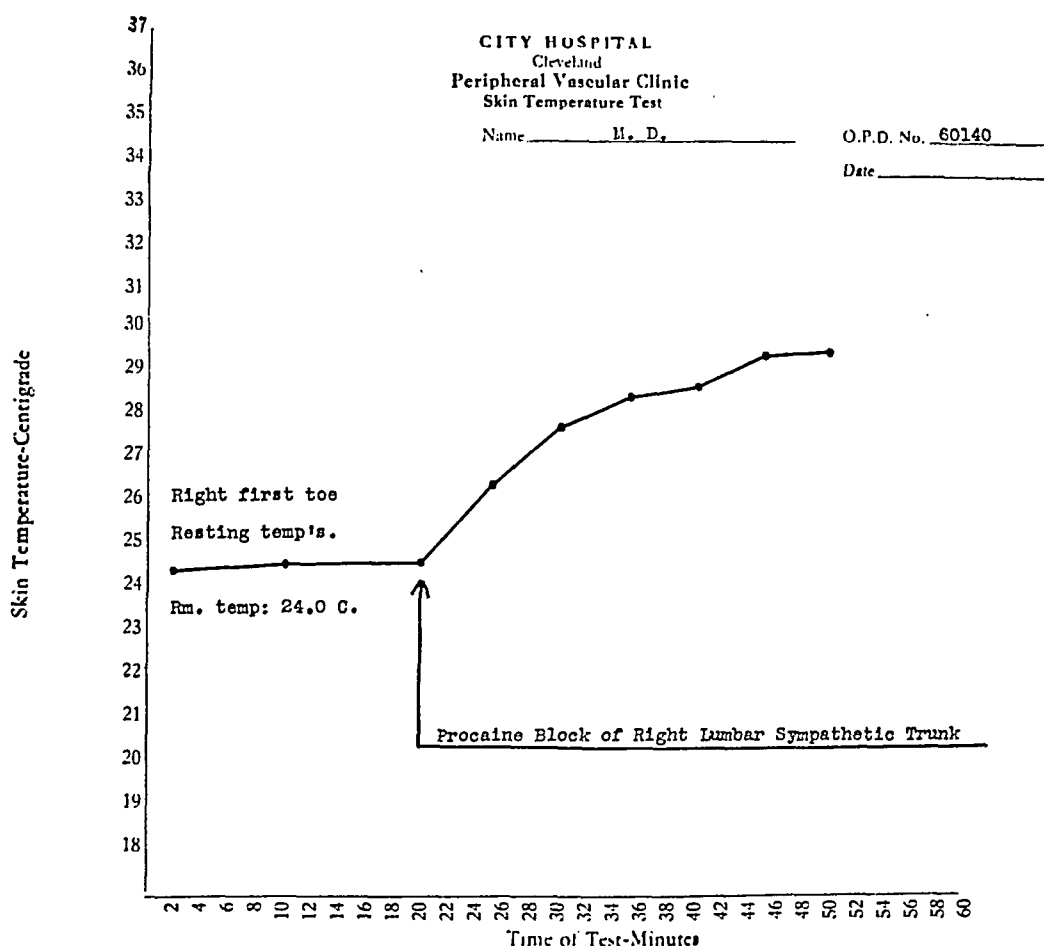


Fig. 1.—Figure shows rise in skin temperature of right foot after procaine block of lumbar sympathetic trunk.

At the present writing, twenty lumbar sympathectomies have been performed in cases of this kind. Of these patients, twelve have been observed for a period of a year or longer. The results obtained are summarized in Table I. (A year of observation is considered the minimum for drawing valid conclusions concerning the benefit derived from any form of treatment in peripheral arteriosclerotic disease.) Following operation, these patients received no further therapy except that associated with the routine care of the feet or the local treatment of ulceration. Clinically, these cases have been characterized preoperatively by an absence of marked pallor of the foot on elevation or rubor on dependency,

by soft, pliable skin and subcutaneous tissue, usually, but not always, by some degree of pulsation in the lower leg, as measured with the oscillometer, by a venous filling time of not more than fifteen seconds, by severe subjective and objective coldness of the foot, and by a rapid rise in the skin temperatures of all the toes to a vasodilatation level of at least 28°C . after procaine block of the sympathetic nervous pathways to the blood vessels of the foot, and by the failure of conservative treatment to ameliorate symptoms or to heal ulceration. In short, they were cases in which the collateral vascular network was not incapable of hypertrophy, and in which the small vessel bed had retained its flexibility. The following detailed reports illustrate what can be expected in this type of case in the way of relief of symptoms, healing of ulcerations, and increase in the vascular reserve through hypertrophy of a collateral circulation when vasoconstrictor tone is removed surgically.

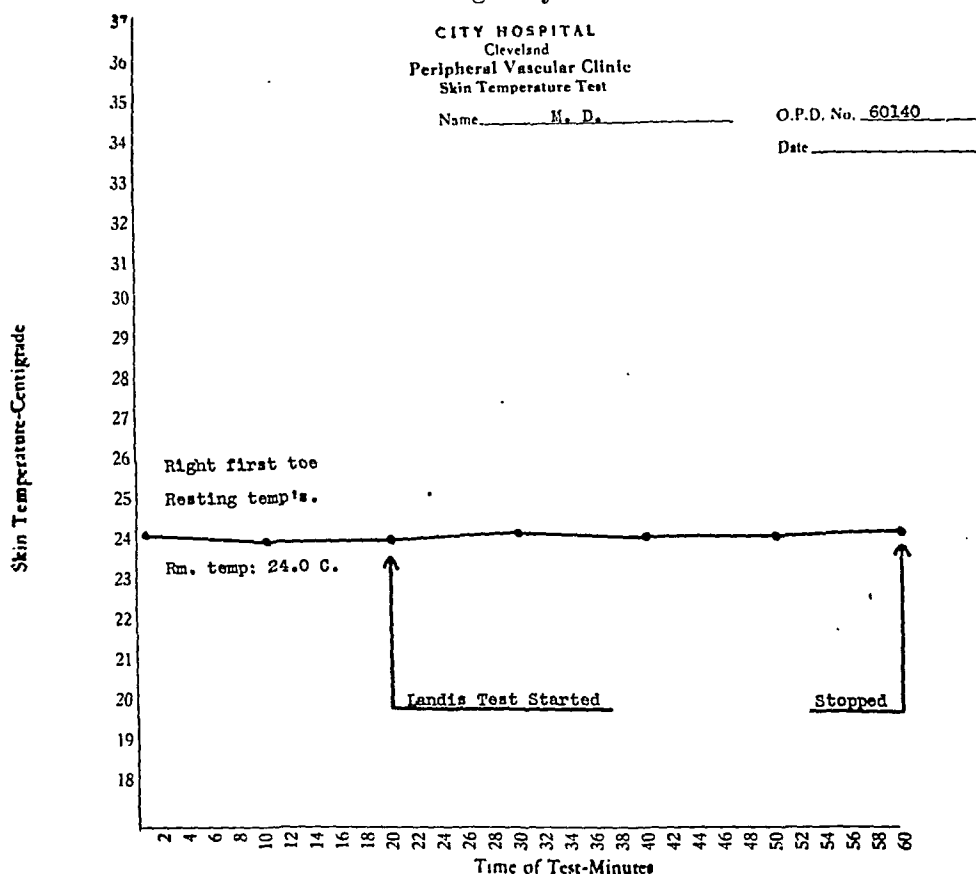


Fig. 2.—Illustration shows failure of powerful vasodilating measure, the Landis test, to duplicate the rise in skin temperature obtained with procaine block of sympathetic vasoconstrictor impulses to blood vessels of foot.

The first has to do with the relief of severe, persistent coldness, numbness, and paresthesias. After lumbar sympathectomy the disappearance of such symptoms is immediate. Not uncommonly, on the day after the operation, the patient remarks that for the first time in years the sympathectomized foot feels "alive."

TABLE I

SUMMARY OF CASES OF PERIPHERAL ARTERIOSCLEROTIC DISEASE IN WHICH LUMBAR SYMPATHECTOMY WAS DONE AND THE PATIENT OBSERVED FOR PERIOD OF TWELVE MONTHS OR LONGER

PREOPERATIVE OBSERVATIONS										POSTOPERATIVE STATUS				
NO.	EX-TREMITY	AGE (YR.)	DORS. PED.	POST. TIB.	SKIN TEMP.*	OSCILLO-METRIC RDGS.†	SYMPTOMS	INTER-VAL (MO.)	DORS. PED.	POST. TIB.	SKIN TEMP.	OSCILLO-METRIC RDGS.	SYMPTOMS	
1	P. B.	56	Absent	Absent	22.0	0.2	Severe int. cl.; cold, numb foot	12	Absent	Absent	33.0	1.0	Slight fatigue at end of full day's work	
2	P. B.	56	Absent	Absent	22.0	0.5	Severe int. cl.; cold, numb foot	12	Absent	Absent	33.5	2.5	None	
3	O. C.	68	Absent	Absent	23.0	1.0	Painful ulcers on fourth and fifth toes	12	Absent	Absent	32.5	2.5	None; ulcers healed	
4	I. M.	56	Absent	Absent	25.0	0.2	Severe int. cl.; cold, numb foot	12	Absent	Absent	32.5	2.3	Slight fatigue only with rapid walking	
5	E. G.	57	Weak	Absent	22.0	1.5	Severe int. cl.; cold, numb foot	14	Weak	Absent	33.0	3.0	None	
6	E. G.	57	Absent	Absent	22.0	1.0	Severe int. cl.; cold, numb foot	14	Absent	Absent	32.0	2.0	Slight fatigue at end of full day's work	
7	J. G.	60	Absent	Absent	22.5	0.0	Severe int. cl.; cold, numb foot	17	Absent	Absent	32.0	1.5	None	
8	O. H.	55	Absent	Absent	24.0	0.0	Severe int. cl.; cold, numb foot	17	Absent	Absent	30.5	0.5	Intermittent claudication not improved	
9	A. F.	61	Absent	Absent	23.0	0.5	Severe int. cl.; cold, numb foot	18	Absent	Absent	32.0	1.5	Slight fatigue after walking long distance	
10	S. B.	58	Absent	Absent	22.0	0.1	Painful ulcer in nail bed of first toe; cold foot; severe int. cl.	20	Absent	Absent	30.0	0.5	None in foot; ulcer healed; intermittent claudication not improved	
11	K. S.	57	Weak	Weak	22.5	1.5	Painful, cold, numb foot	21	Weak	Weak	32.5	2.5	None	
12	K. S.	57	Absent	Absent	22.5	1.0	Painful, cold, numb foot	25	Absent	Absent	32.0	2.0	None	

*Skin temperatures from pad first toe at room temperatures (22.0° to 24.0° C.).

†Oscillometric readings taken at supramalleolar level.

CASE 80371.—K. S., a white, female diabetic, aged 57, came under observation May 6, 1938. For three years, even in warm weather, she had suffered from severe coldness, numbness, and paresthesias of the feet. During this period she took daily warm foot baths and vasodilating drugs without relief. Lately, the symptoms had become more severe, a burning type of pain had appeared in her feet, and she was threatened with incapacitation. Examination showed that the pulsation in the right dorsalis pedis and posterior tibial arteries was barely palpable, and no pulsation was felt in the left dorsalis pedis and posterior tibial arteries. Oscillometric examination revealed a diminution of pulsation in the region of the lower legs. Roentgenograms showed calcification in the long arteries of the legs. There were no marked color changes, and the nutritional status of the feet was good. At a room temperature of 24° C., both feet were cold to the touch, but, after procaine block of both lumbar sympathetic trunks, they warmed rapidly; the skin temperatures of the toes reached vasodilatation levels ranging from 30° C. to 32° C. The procaine blocks gave considerable subjective relief for a few hours, and therefore an alcohol block of the left lumbar sympathetic trunk was done. This gave complete relief of symptoms for three weeks. However, at the end of that time the beneficial effects of the block waned, and all of the symptoms returned. The block was not repeated because the first one resulted in an alcoholic neuritis of the lateral cutaneous nerve of the thigh (this will be again referred to later in the paper). A left-sided lumbar sympathectomy was performed in June, 1938. The operation gave immediate and complete relief of all symptoms in the left foot. She returned voluntarily to the Clinic in October, 1938, asking that the right foot also be sympathectomized. When last seen, in July, 1940, she stated that her feet had been symptom free since the operation. The skin temperatures of the toes ranged between 30° C. and 32° C. A faint pulsation was still palpable in the right dorsalis pedis and posterior tibial arteries. The oscillometric readings in both legs had almost doubled their preoperative magnitude.

In some cases of painful ulceration of the affected limb, sympathectomy may expedite the healing of the ulceration and gradually relieve the pain. The following cases illustrate the relief of pain associated with ulceration.

O. C., a 68-year-old white woman, was first seen on July 21, 1939. For nine months she had been suffering from increasingly severe pain, subjective coldness, numbness, and paresthesias of the left foot. More recently, ulcers had appeared on the fourth and fifth toes of the left foot. Examination showed that no pulsation was palpable in the left dorsalis pedis or posterior tibial artery. Oscillometric study revealed diminished pulsation in the region of the lower leg. No marked color changes were present except for some cyanosis of the fourth and fifth toes, which were superficially ulcerated. There was no atrophy of the skin or subcutaneous tissue. At a room temperature of 24° C., the foot was very cold to the touch, but, after procaine block of the posterior tibial nerve, the foot became palpably warm, and the skin temperatures of the toes rose to vasodilatation levels ranging from 29° C. to 30° C. During the following three months she received intravenous injections of calcium gluconate and short-wave diathermy to the left foot twice a week, and daily, warm, leg baths, followed by treatment with the intermittent venous occlusion cuff at home. This treatment gave no relief from the symptoms, which became increasingly severe, and the ulceration of the toes progressed. Despite her age, she appeared to be a good operative risk, and a left-sided lumbar sympathectomy was performed in October, 1939. During the two months immediately following the operation there was a gradual decrease in the severity of symptoms, accompanied by healing of the ulcerations. Six months after the operation she was symptom

free, and the ulcerations had completely healed. The foot was warm and dry, had a good color, and appeared normal in every way. In October, 1940, twelve months after sympathectomy, the improvement had been maintained. The skin temperatures of the toes ranged from 31.0° C. to 32.5° C.

S. B., a 58-year-old white man, was seen Feb. 21, 1939. For a year he had suffered continuous, excruciating pain in his right great toe, and persistent, severe, subjective coldness and numbness of the right foot. The painful toe was ulcerated. During this year he had received intravenous injections of hypertonic saline with no relief. Examination showed that no pulsation was palpable in the right dorsalis pedis or posterior tibial artery. Oscillometric study revealed a slight trace of pulsation in the region of the lower leg. There were no marked color changes except for some cyanosis of the right great toe, which was ulcerated along the margins of the nail. There was no atrophy of the skin or subcutaneous tissue. At a room temperature of 24° C., the foot was cold to the touch and covered with perspiration. After procaine block of the posterior tibial nerve, the foot became palpably warm, and the skin temperatures of the toes rose to vasodilatation levels ranging from 29° C. to 30° C. During the following two months he received additional conservative therapy consisting of warm leg baths twice a day, whiskey, and treatment with the intermittent venous occlusion cuff. He also received intravenous injections of 5 per cent saline twice a week. No relief of symptoms was obtained, and, in April, 1939, a right-sided lumbar sympathectomy was performed. During the following two months complete healing of the ulceration, with relief of symptoms, took place. In October, 1940, the skin temperatures of all the toes ranged between 31° C. and 31.5° C. The nutritional status of the right foot appeared to be good.

There is some difference of opinion regarding the beneficial effects of sympathectomy in cases of ischemic muscular pain, the so-called intermittent claudication. I do not believe that lumbar sympathectomy is ever indicated in the treatment of intermittent claudication per se, because such pain does not, in itself, indicate an ischemic condition the nature of which jeopardizes the structural integrity of the limb. However, the question arises as to what effect lumbar sympathectomy has on ischemic muscular pain when it is present in the kind of case under discussion. There is some experimental evidence¹⁻⁴ which appears to indicate that the circulation through peripheral muscle tissue is not influenced by sympathetic vasoconstrictor impulses, and that, therefore, lumbar sympathectomy should have no effect on intermittent claudication. However, Grimson and Shen⁵ tested the vasomotor responses of skinned legs, and report directly opposite conclusions. In the group of cases summarized in Table I, intermittent claudication disappeared or became markedly diminished in seven out of nine instances following lumbar sympathectomy (see Table I). The presence of a few, very small, sclerotic muscle vessels without distal anastomotic connections, with an available collateral circulation, could have been responsible for the two failures. Only a small quantity of muscle tissue need be ischemic to give rise to considerable pain. As Kellgren⁶ has recently shown, a very minute quantity of an irritating substance, e.g., 5 minims of 6 per cent saline, when injected directly into muscle tissue, produces

intense pain which is felt not only at the site of injection, but over widespread adjacent cutaneous areas as well.

The relief of intermittent claudication, when it was obtained, followed a definite pattern. An immediate increase in walking capacity was rarely observed. However, the cramp-like pain was often replaced at once by a feeling of severe fatigue. As a collateral circulation developed, walking capacity gradually increased. At times, it took a year for the maximum benefit to be obtained. The following two cases not only illustrate relief of intermittent claudication, but also present demonstrable oscillometric evidence of the growth of a collateral circulation following lumbar sympathectomy.

CASE 40982.—J. G., a 60-year-old white man, was admitted to the Peripheral Vascular Clinic at the Cleveland City Hospital on Jan. 27, 1939. During the previous year he had suffered severe aching pain, subjective coldness, and numbness of the left foot. Intermittent claudication was also present, involving the left calf and foot. He could walk only two blocks before the onset of muscular cramps forced him to stop and rest. Examination showed no marked color changes or atrophy of the skin or subcutaneous tissue of the left foot. No pulsation was palpable in the left dorsalis pedis or posterior tibial artery. Oscillometric readings at the level of the lower leg were zero. At a room temperature of 24° C., the foot was very cold, but, after procaine block of the left lumbar sympathetic trunk, the foot warmed rapidly, and the skin temperatures of all the toes rose to vasodilatation levels ranging from 30° C. to 31° C. A left-sided lumbar sympathectomy was performed in February, 1939. One month after sympathectomy the foot symptoms were completely relieved. However, his walking capacity had not increased, although he now experienced severe fatigue instead of the cramp-like pain he had felt prior to the operation. Oscillometric readings at the level of the lower leg were still zero. Three months later he was able to walk a much longer distance before the onset of fatigue. At this time the oscillometer registered a trace of pulsation in the region of the lower leg. He was seen at regular intervals during the following year, and, in July, 1940, seventeen months after the operation, all his symptoms, including the intermittent claudication, had disappeared. The nutritional status and color of the foot were excellent. The skin temperatures of the toes ranged from 32° C. to 33° C. There was still no palpable pulsation in the dorsalis pedis and posterior tibial arteries. However, the oscillometer now revealed an excellent pulsation in the same segment of the leg where none was present prior to the sympathectomy. This marked increase in pulsation, which developed gradually during the seventeen months following sympathectomy, is illustrated in the oscillometric tracings shown in Fig. 3. Since there is no reason to believe that sympathectomy restores elasticity to arteries which are already diseased, such an increase in magnitude can only be interpreted as the result of hypertrophy of healthy collateral arteries.

I. M., a 56-year-old white man, was seen Aug. 12, 1938. For several months he had suffered from subjective coldness of the right foot, and from aching, cramp-like pains in the muscles of his right calf which appeared on walking. He could walk only a few blocks before the onset of pain forced him to rest. Examination showed that there were no color changes or atrophy of the skin or subcutaneous tissue of the right foot. No pulsation could be felt in the right dorsalis pedis and posterior tibial arteries. A roentgenogram showed calcification of the dorsalis pedis artery. The oscillometer revealed only a trace of pulsation in the region of the right lower leg. At a room temperature of 24° C., the foot was cold to the touch, but, after procaine block of the posterior tibial nerve, the foot warmed rapidly, and the skin

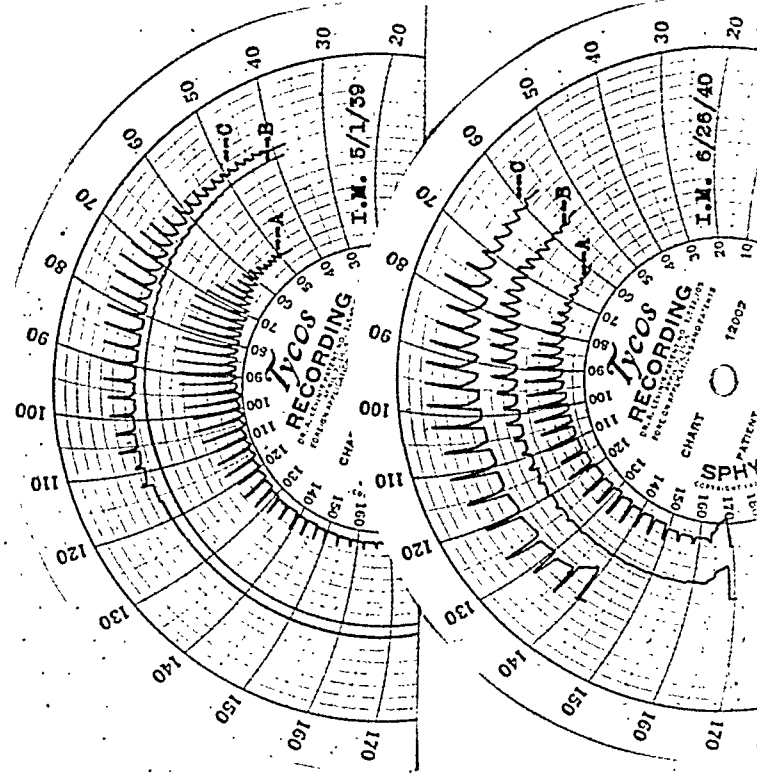


Fig. 4.—Illustration shows marked increase in magnitude of pulsation in region of right lower leg during the twelve-month period following lumbar sympathectomy. Note decrease in magnitude of arterial pulsation in opposite lower leg during this same period to a point where it was less than that in the lower forearm. This indicates beginning arteriosclerotic disease in the left lower extremity.¹⁰ A, Left lower leg; B, right lower leg; C, right lower forearm. Upper tracing was taken before right lumbar sympathectomy; lower tracing was taken twelve months after sympathectomy.

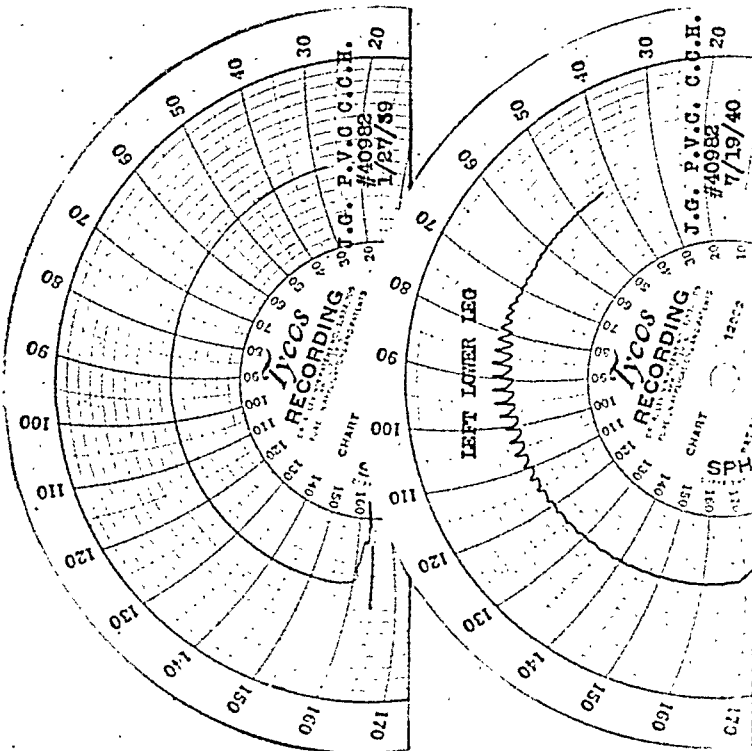


Fig. 3.—Illustration shows increase in magnitude of pulsation in region of lower leg which occurred gradually during a period of seventeen months following lumbar sympathectomy. Such an increase can be interpreted only as the result of hypertrophy of a collateral circulation. Upper tracing was taken before left lumbar sympathectomy; lower tracing was taken seventeen months after sympathectomy.

temperatures of the toes reached vasodilatation levels ranging from 32° C. to 33° C. During the following eight months he received intensive conservative vasodilating therapy without relief. This treatment included whiskey and daily, warm, leg baths, followed by treatment with the intermittent venous occlusion cuff, short-wave diathermy, intravenous injections of hypertonic saline, and the administration of



Fig. 5.—Arrows indicate shadows of silver clips on severed ends of lumbar sympathetic trunk. Note that trunk has been severed at upper pole of third lumbar vertebra, and that the caudal portion has been buried in adjacent psoas muscle. This procedure denervates the cutaneous vessels of the foot and lower two-thirds of the leg, and the popliteal artery and its deep branches.

deproteinated pancreatic extract. In May, 1939, a right-sided lumbar sympathectomy was performed. He was seen one month after operation. At this time the foot symptoms had disappeared, but his walking capacity had not increased. However,

he now experienced severe fatigue instead of cramps. Oscillometric examination at this time showed no increase in the magnitude of pulsation in the region of the lower leg. He was not seen again until July, 1940, fourteen months after the sympathectomy. At this time, walking at a moderate rate of speed caused no fatigue. The color and nutritional status of the foot were normal. The skin temperatures of the toes ranged from 31.5°C . to 32.5°C . No pulsation could be felt in the dorsalis pedis or posterior tibial arteries. However, the oscillometric reading now revealed a definite pulsation in the same segment of the leg where only a trace had been present prior to the sympathectomy (Fig. 4).

Table I lists the oscillometric readings which were taken at the level of the lower leg immediately preceding sympathectomy, and after a postoperative interval of twelve to twenty-five months. It will be noted that some degree of increase in the magnitude of the pulsation occurred in every instance. For reasons stated, this is construed as valid evidence of the hypertrophy of a collateral arterial network. In none of these cases was an increase in the magnitude of pulsation observed immediately after sympathectomy. This rules out the possibility that these increases in the magnitude of pulsation were the result of a simple diminution in the tonus of the vessels, rather than an actual hypertrophy of collateral arteries.

The surgical technique used to denervate these extremities has been described elsewhere.⁷ It is a simplified form of lumbar sympathectomy. Briefly, the technique is as follows. Through a muscle-splitting extra-peritoneal approach, as described by Pearl,⁸ the lumbar sympathetic trunk is exposed on the upper pole of the third lumbar vertebra at the inner margin of the psoas major muscle. The trunk is divided at this point, and the distal, cut end is stripped from the body of the third lumbar vertebra and buried in the adjacent psoas muscle (Fig. 5). The operation is easily and quickly performed, and causes no more shock than an appendectomy or simple herniorrhaphy. The blood vessels which are denervated by this procedure are the popliteal artery and its deep branches, and the cutaneous vessels of the foot and lower two-thirds of the leg.

I have discontinued the use of paravertebral alcohol block of the lumbar sympathetic ganglia. Too often, an alcoholic neuritis of the lateral cutaneous nerve of the thigh has occurred. The resultant pain has been as disabling as that for the relief of which the block was done.

I should like to express my appreciation to Dr. Roy W. Scott for his advice and criticism, and to his associates for their cooperation in deciding whether or not these patients were operable.

REFERENCES

1. Grant, R. T., and Pearson, R. S.: Blood Circulation in the Human Limb, Clin. Sc. 3: 119, 1938.
2. Grant, R. T.: Observations on Blood Circulation in Voluntary Muscles in Man, Clin. Sc. 3: 157, 1938.
3. Abramson, D. I., and Ferris, E. B.: Responses of Blood Vessels in Resting Hand and Forearm to Various Stimuli, AM. HEART J. 19: 541, 1940.

4. Friedlander, M., Silbert, S., and Bierman, W.: The Regulation of Circulation in the Skin and Muscles of the Lower Extremity, *Am. J. M. Sc.* 199: 657, 1940.
5. Grimson, K. S., and Shen, T. R.: Vasomotor Responses to Adrenalin and to Carotid Sinus Impulses in Normal, Skinned, and Denervated Legs, *Arch. internat. de pharmacodyn. et de therap.* 63: 95, 1939.
6. Kellgren, J. H.: Observation on Referred Pain Arising From Muscle, *Clin. Sc.* 3: 175, 1938.
7. Atlas, L. N.: A Modified Form of Lumbar Sympathectomy for Denervating the Blood Vessels of the Leg and Foot; A Preliminary Report, *Ann. Surg.* 111: 117, 1940.
8. Pearl, F. L.: Muscle Splitting Extraperitoneal Ganglionectomy, *Surg., Gynec., & Obst.* 65: 107, 1937.
9. Atlas, L. N.: Oscillometry in the Diagnosis of Arteriosclerosis of the Lower Extremities; A New Method of Application, *Arch. Int. Med.* 63: 1158, 1939.
10. Atlas, L. N.: Significance and Interpretation of Oscillometric Readings in Peripheral Arteriosclerotic Disease, *Arch. Int. Med.* 66: 155, 1940.

10465 CARNEGIE AVENUE

THE EFFECT OF DIFFUSE PERICARDITIS ON THE ELECTROCARDIOGRAPHIC PATTERN OF RECENT MYOCARDIAL INFARCTION

R. LANGENDORF, M.D.
CHICAGO, ILL.

THE criteria for the electrocardiographic diagnosis of diffuse pericarditis complicating recent myocardial infarction were formulated by Barnes,¹ who pointed out that the reciprocal relationship between Leads I and III which is found in classical cases of uncomplicated recent myocardial infarction is absent. When pericarditis occurs in cases of recent myocardial infarction, he states, elevation of S-T in one of these leads with depression in the other, or an upright coronary T in one of these leads with an inverted one in the other, is usually not found. Instead, the S-T segment is elevated in all the limb leads, and, later, T may become inverted in all limb leads. Recently the subject was reviewed by Winternitz and Langendorf,² who collected from the literature twenty-two cases of recent myocardial infarction with an electrocardiographic pattern similar to that reported by Barnes; in these cases a pericardial friction rub had been observed clinically or pericarditis had been found at necropsy, and to these they added three autopsy cases of their own. It would appear that the special modifications of the electrocardiographic pattern when there is a complicating pericarditis are limited to the generalized form. Localized pericarditis limited to a small area over the infarct does not seem to cause modifications of the S-T-T pattern which would be anticipated from the infarct itself. This is in accord with the effect on the electrocardiogram of experimental ligation of the coronary arteries of the dog and of localized pericarditis (Barnes and Mann,³ Burchell, Barnes, and Mann⁴). Diffuse pericarditis complicating myocardial infarction is not an uncommon occurrence. Thus, Stewart and Turner⁵ found ten cases (16.6 per cent) of generalized pericarditis in sixty autopsy cases of myocardial infarction; Saphir, Priest, Hamburger, and Katz⁶ observed four out of thirty-four cases (11.7 per cent); Bohning and Katz⁷ noted three out of twenty-seven cases (11.1 per cent); Jervell⁸ recorded five out of twenty-six cases (19.2 per cent); and Büchner, Weber, and Haager⁹ found two out of nine autopsy cases (22.2 per cent). Thus, out of 156 autopsy cases of recent myocardial infarction which have been reported, there was a complicating, diffuse pericarditis in twenty-four (15.3 per cent).

However, there is a lack of sufficient data in the literature on the changes in the electrocardiogram of recent myocardial infarction which

From the Cardiovascular Department, Michael Reese Hospital, Chicago, Ill.
Aided by the A. D. Nast Fund for Cardiac Research.
Received for publication Sept. 6, 1940.

are produced by complicating, diffuse pericarditis. It might be anticipated that, when diffuse pericarditis complicates recent myocardial infarction, the electrocardiogram would take on some of the changes which occur in diffuse pericarditis without infarction, as described by Winternitz and Langendorf,² among others, or at least that it would show a composite of the contour seen in the two conditions. In this paper we wish to report observations upon two additional autopsy cases, and to discuss the significance of similar changes in cases in which the diagnosis was not proved by autopsy. The latter is important because it is known that the classical electrocardiographic pattern of infarction, with discordancy of the S-T-T segments in Leads I and III, does not always

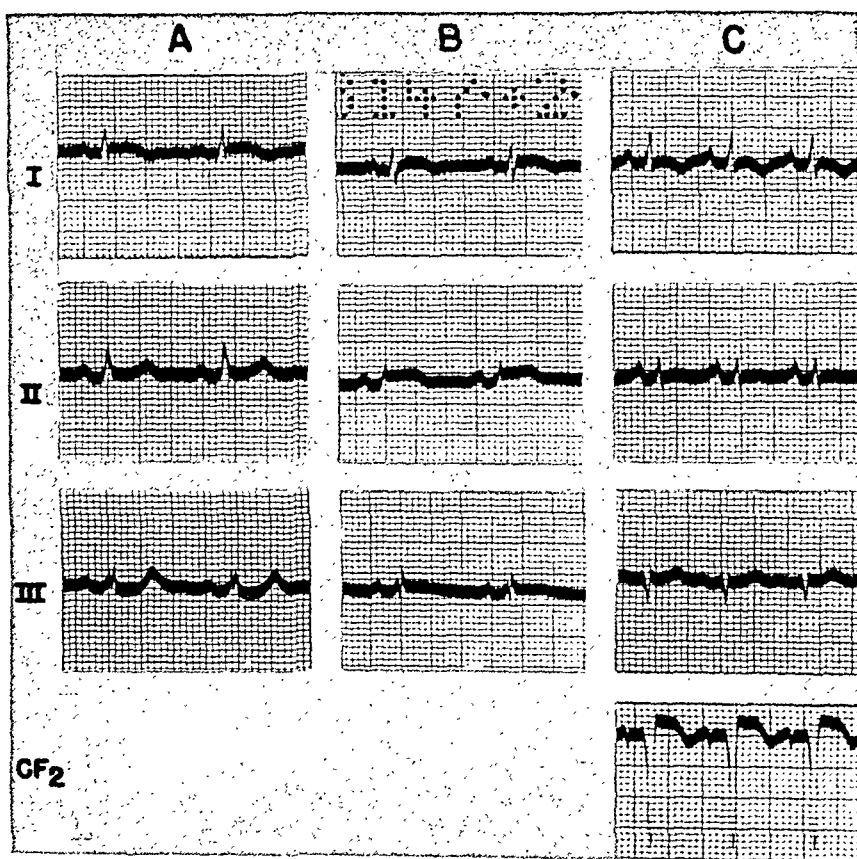


Fig. 1.—(Case 1.) The patient had four severe attacks of angina pectoris between April 20, 1933 and May 4, 1933. Record A was taken on May 4, 1933, B on May 8, 1933, C on May 31, 1933. Autopsy, June 2, 1933, revealed recent infarction of the apical portion of the left ventricle and diffuse fibrinous pericarditis, with obliteration of the entire pericardial sac. Records A and C show changes of the anterior wall type; A shows discordant S-T changes in Leads I and III, C shows discordant T changes in Leads I and III. Record B shows a transient concordant elevation of the S-T segment in all limb leads.

occur. This has been emphasized in publications from this department (Bohning and Katz,⁷ Weinberg and Katz¹⁰). A number of reasons have been advanced by Weinberg and Katz¹⁰ to account for the variations from the classical pattern of recent myocardial infarction, and these deviations in pattern may, in the absence of diffuse pericarditis, bear some resemblance to the curves to be expected with this complication.

METHOD OF STUDY

In order to see whether the criteria for the electrocardiographic diagnosis of diffuse pericarditis complicating recent myocardial infarction could be made more precisely, the electrocardiograms in 380 consecutive cases of what was diagnosed as recent myocardial infarction were examined. From these, thirty-nine cases were selected, including the two with autopsies already referred to, in which there were changes suggesting the possibility of a complicating diffuse pericarditis, and in which these changes could not be attributed to preponderant ventricular hypertrophy or intraventricular block.

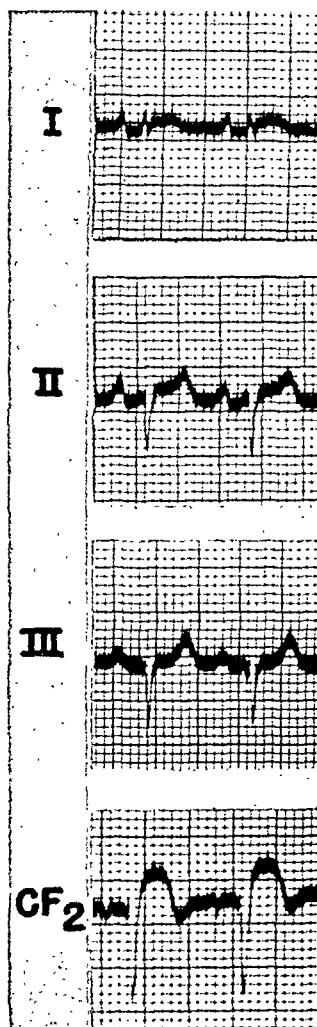


Fig. 2.—(Case 2.) The patient had the attack on May 18, 1935, and a pericardial friction rub was heard on May 23, 1935. The record was taken on May 23, 1935. Autopsy, June 10, 1935, revealed an organizing infarct of the septum and of the anterior wall and of the apex of the left ventricle, with organizing, diffuse, adhesive pericarditis. The electrocardiogram shows an anterior wall infarction pattern in the S-T stage, with no discordant S-T changes in Leads I and III.

The criteria which were used fell into one or more of the following three groups:

1. Concordant elevation of S-T in the limb leads.
2. Concordant inversion of a coronary type of T wave in the limb leads.

3. Absence of a discordant deviation of S-T in Leads I and III, with a marked S-T elevation in one of these leads, i.e., S-T₁ isoelectric and S-T₃ markedly elevated, or vice versa.

A summary of the protocols of these thirty-nine cases is shown in Table I. The cases were next subdivided into four groups, according to the type of the S-T-T pattern in the limb leads and the QRS pattern in these and in chest leads CF₂ and CF₄, as well. The subdivisions were:

1. Anterior wall type of myocardial infarction.
2. Posterior wall type of myocardial infarction.
3. Combined anterior and posterior wall types.
4. Atypical types.

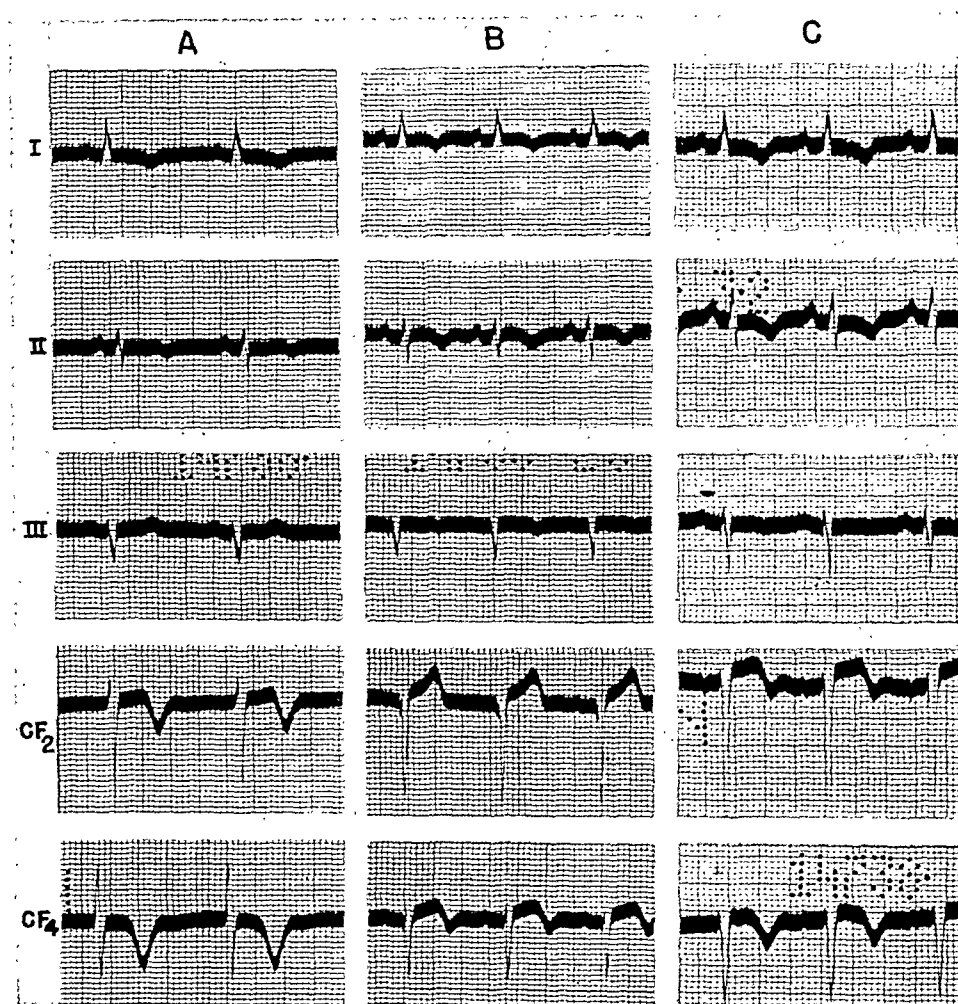


Fig. 3.—(Case 9.) The patient had an attack on June 12, 1939, and a pericardial friction rub was heard on June 20, 1939. Record *A* was taken on June 16, 1939, *B* on June 28, 1939, *C* on August 1, 1939. The electrocardiograms show changes of the anterior wall type. However, the T wave became inverted in all limb leads. For discussion, see text.

Each was further divided into the S-T and T stages. The criteria used for each, the number of cases in each group, the number of autopsies, and the figure illustrating a typical example are assembled in Table II.

TABLE I

CASE	CLASSIFICATION SEE TABLE II	ILLUS. IN FIG.	SEX	AGE	PERI- CARDIAL FRICTION RUB HEARD	AUTOPSY	DATE OF ATTACK	DATE OF ELECTRO- CARDIO- GRAMS	S-T STAGE	T STAGE	EVOLU- TION OF "T _N "	S-T AND T IN CHEST LEADS
1	1A	1	M	49	-	6/2/33 Infarction of the apex of the left ventricle, with diffuse pericar- ditis.	4/20/33 5/ 4/33	5/ 4/33 5/ 8/33 5/16/33 5/31/33	concord- ant	discord- ant	-	CF ₂ anterior wall type
2	1A	2	M	42	5/23/35	6/10/35 Infarction of the sep- tum, anterior wall, and apex of the left ven- tricle, with diffuse ad- hesive pericarditis.	5/18/35	5/23/35	absence of dis- cord- ance	-	-	CF ₂ anterior wall type
3	1A	-	M	53	-	-	4/26/39	5/ 1/39 5/ 3/39	concord- ant	-	-	CF ₂ , CF ₄ anterior wall type
4	1A	-	M	67	-	-	10/ 5/37	10/ 8/37 10/18/37	concord- ant	discord- ant	-	CF ₂ anterior wall type
5	1A	-	M	49	2/25/36	-	2/23/36	2/28/36 3/ 2/36 3/31/37	concord- ant	discord- ant	-	CF ₂ anterior wall type
6	1A & B	-	M	37	6/10/31	-	6/ 1/31	6/ 8/31 6/18/31 7/ 1/31 7/10/31 7/18/31	concord- ant	concord- ant	4 weeks	-
7	1A	-	M	65	-	-	10/11/36	10/16/36 10/19/36	concord- ant	-	-	CF ₂ anterior wall type; S-T elevation more marked when S-T elevated in all limb leads

8	1A & B	-	F	55	4/ 1/31	-	3/31/32	1/ 7/31 4/ 1/32 4/ 5/32 4/18/32 4/26/32 5/ 2/32	concord- ant	concord- ant	2 days, S-T still elevated	
9	1B	3	M	65	6/20/39	-	6/12/39	6/16/39 6/28/39 8/ 1/39	-	concord- ant	16 days	CF ₂ , CF ₄ anterior wall type
10	1B	-	M	66	-	-	2/20/37 ?	3/10/37 3/23/37	-	concord- ant	5 weeks	CF ₂ anterior wall type
11	1B	-	M	59	-	-	11/29/36	12/ 2/36 12/ 5/36 12/11/36 12/18/36 12/23/36 12/30/36 1/22/37	discord- ant	concord- ant	13 days	CF ₂ S-T elevated, T up- right and pointed
12	1B	-	F	50	-	-	?	2/ 9/39 3/24/39 7/27/39	-	concord- ant	?	CF ₂ , CF ₄ T in CF ₂ upright, in CF ₄ inverted
13	1B	-	F	60	-	-	9/22/38 to 9/28/38	9/30/38 10/ 3/38 10/12/38 10/24/38 11/ 8/38 6/22/38	-	concord- ant	1 week	CF ₂ , CF ₄ anterior wall type
14	2A & B	4	M	65	6/15/38	-	6/12/38	6/14/38 6/16/38 6/27/38 6/30/38	concord- ant	concord- ant	2 weeks	CF ₂ , CF ₄ S-T depression re- duced when S-T elevated in all limb leads; T in CF ₂ up- right, in CF ₄ invert- ed

TABLE I—CONT'D

CASE	CLASSIFI- CATION SEE TABLE II	ILLUS. IN FIG.	SEX	AGE	PERI- CARDIAL FRICTION RUB HEARD	AUTOPSY	DATE OF ATTACK	DATE OF ELECTRO- CARDIO- GRAMS	S-T STAGE	T STAGE	EVOLU- TION OF "T _N "	S-T AND T IN CHEST LEADS
15	2A	-	M	66	5/29/40	-	5/26/40	5/29/40 5/31/40 6/7/40	concord- ant	-	-	CF ₃ , CF ₄ S-T depression re- duced when S-T leads; T upright and tall
16	2A	-	M	65	6/15/38	-	6/12/38	6/14/38 6/16/38 6/27/38 6/30/38	concord- ant	discord- ant	-	-
17	2A	-	M	74	-	-	10/24/36	10/27/36	concord- ant	-	-	-
18	2A	-	F	60	-	-	12/9/35	12/10/35	concord- ant	-	-	CF ₃ S-T ₂ isoelectric, T up- right
19	2A	-	M	27	-	-	3/19/40	3/19/40 3/21/40 3/30/40 4/27/40	concord- ant	-	-	CF ₃ posterior wall type
20	2A & B	M	41	-	-	-	8/23/36	8/24/36 8/26/36 9/10/36 9/23/36	concord- ant	discord- ant	-	CF ₃ , CF ₄ S-T depression re- duced when S-T leads; T upright and tall
21	2A & B	F	59	-	-	-	9/11/36	9/12/36 9/14/36 9/25/36 10/12/36	concord- ant	concord- ant	3 days, S-T still elevated	CF ₃ S-T elevated, T up- right and pointed
									concord- ant	2 weeks	CF ₃ posterior wall type	

22	2B	-	M	57	9/21/39	-	?	9/29/31 10/ 3/31 12/19/31	discord- ant	concord- ant	?	-
23	2B	-	M	70	-	-	12/24/31 to 12/30/31	12/30/31 1/ 1/32 1/ 3/32 1/11/32 8/17/33	-	concord- ant	1 week	CF ₂ T upright
24	2B	-	M	63	-	-	?	12/17/35 12/19/35 12/31/35 5/21/36 11/12/36	-	concord- ant	?	CF ₂ T upright
25	2B	-	M	49	-	-	?	1/28/37 2/ 5/37 2/23/37	-	concord- ant	?	CF ₂ T upright
26	3A & B	5	M	52	6/14/36	-	6/ 9/36 and fol. days	6/13/36 6/22/36 6/29/36 7/ 5/36 7/13/36 7/20/36 6/ 2/38	concord- ant	concord- ant	5 weeks	CF ₂ anterior wall type
27	3A & B	-	M	50	-	-	12/22/39	12/22/39 12/22/39 12/25/39 1/ 8/40 1/27/40 3/ 5/40 3/ 6/40	concord- ant	concord- ant	4 days S-T still elevated	CF ₂ , CF ₄ anterior wall type

TABLE I—CONT'D

CASE	CLASSIFICATION SEE TABLE II	ILLUS. IN FIG.	SEX	AGE	PERI- CARDIAL FRICTION RUB HEARD	AUTOPSY	DATE OF ATTACK	DATE OF ELECTRO- CARDIO- GRAMS	S-T STAGE	T STAGE	EVOLU- TION OF "T _N "	S-T AND T IN CHEST LEADS
28	3A & B	-	F	50	-	10/18/37 Infarction of the poste- rior septum, posterior and lateral wall of the right ventricle, and of the anterior apex of the left ventricle, with localized fibrous peri- carditis	10/ 9/37	3/12/37 10/11/37 10/13/37	concord- ant	concord- ant	5 days	CF ₂ , CF ₄ anterior wall type
29	3A & B	-	M	34	-	-	-	-	-	-	-	-
30	3A & B	-	M	62	-	-	12/16/35	12/19/35 12/21/35	concord- ant	concord- ant	5 days, CF ₂ S-T still elevated	S-T elevated, T up-
31	3A	-	M	59	-	-	?	8/13/31	concord- ant	concord- ant	?	right
32	3B	-	M	52	10/ 1/36	-	12/12/35	12/23/35 12/30/35 1/ 7/36	concord- ant	-	-	-
33	3B	-	M	59	-	11/21/31 Infarction of the apex and posterior wall of the left ventricle.	9/21/36	9/24/36 9/29/36 10/ 2/36 10/20/36 4/14/37	discord- ant	concord- ant	11 days	CF ₂ anterior wall type
							1929, 4/17/31 10/20/31 10/28/31 10/30/31	-	-	?	-	-

34	3B	-	M	56	-	-	7/30/36	8/ 1/36 8/ 4/36 8/ 7/36 8/14/36	discord- ant	concord- ant	14 days	CF ₂ anterior wall type
35	3B	-	F	52	-	-	11/15/39	11/21/39 11/24/39 12/ 4/39 12/15/39 1/ 8/40 3/20/40	discord- ant	concord- ant	over 7 weeks	CF ₂ , CF ₄ anterior wall type
36	4A & B	6	M	49	-	-	11/22/37	11/22/37 11/26/37 12/ 6/37 2/26/38	concord- ant	concord- ant	5 days, S-T still elevated	CF ₂ S-T slightly elevated, T notched
37	4A	-	M	59	-	-	6/30/37	7/ 1/37 7/ 3/37 2/20/40	concord- ant	-	-	CF ₂ S-T slightly elevated, T upright
38	4A & B	-	M	58	-	-	8/13/32	8/17/32 8/19/32 8/26/32 8/27/32 9/ 8/32 9/ 9/32 9/15/32 10/22/32	concord- ant	concord- ant	14 days	CF ₂ posterior wall type
39	4B	7	F	44	-	-	4/ 5/39	5/ 5/39 5/ 9/39 5/22/39 7/ 1/39	-	concord- ant	?	CF ₂ , CF ₄ posterior wall type

An analysis of the distribution of the thirty-nine cases showed that in twenty-two instances records were available in both the S-T and T

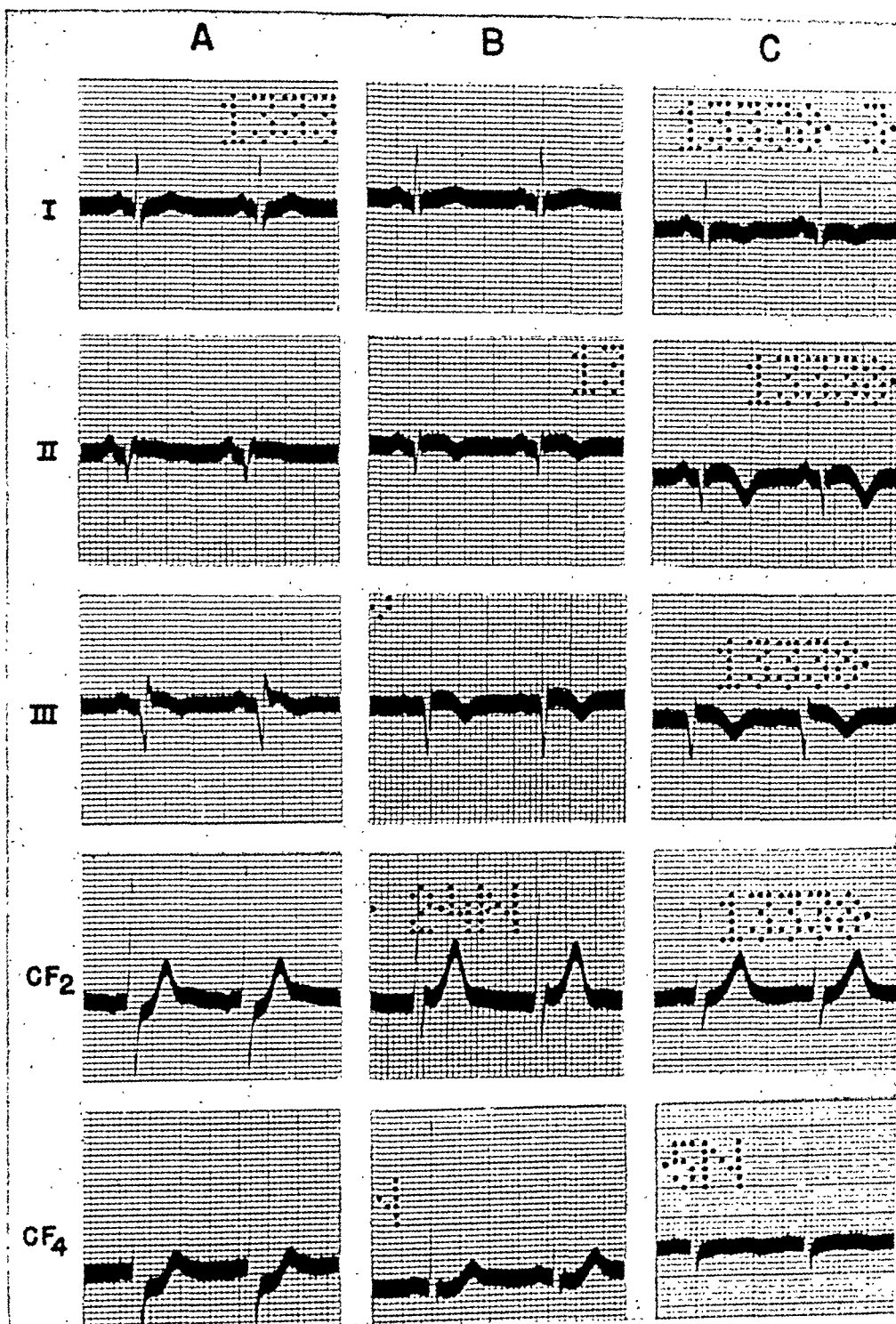


Fig. 4.—(Case 14.) The patient had the attack on June 12, 1938, and a pericardial friction rub was heard on June 15, 1938. Record A was taken on June 14, 1938, B on June 16, 1938, C on June 27, 1938. Record A shows changes of the posterior wall type, with discordant S-T changes in Leads I and III and a marked S-T deviation in the chest leads; B shows a concordant S-T elevation in the limb leads and the disappearance of the S-T depression in the chest leads; C shows a concordant T-wave inversion in the limb leads, an upright T in CF₂ and a small and inverted T in CF₄. For discussion, see text.

stages; in eight, records were obtained only in the S-T stage, and, in nine, only in the T stage. Of the twenty-two patients who were seen during both the S-T and T stages, twelve showed the criteria for special selection in both the S-T and T stages, five showed them only in the S-T, and five only in the T stage. Thus, of the thirty-nine cases, there were thirteen in which the criteria were present in the S-T stage, fourteen in the T stage, and twelve in both the S-T and T stages. The interval between the occurrence of the coronary attack and the appearance of an inverted T wave in all limb leads ("T_N," see Table I) was noted. The significance attached to this interval will be discussed later.

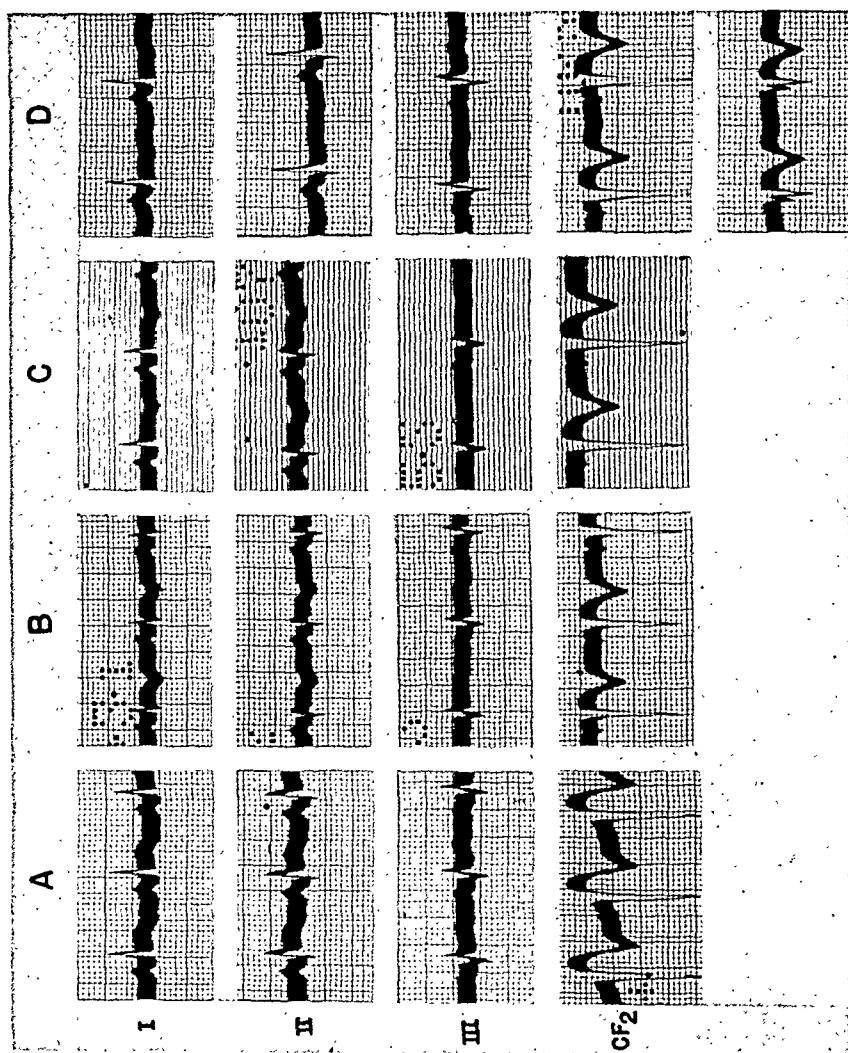


Fig. 5.—(Case 26.) The patient had several severe attacks of angina pectoris, the first on June 9, 1936; a pericardial friction rub was heard on June 14, 1936. Record A was taken on June 13, 1936, B on June 29, 1936, C on July 13, 1936, D on June 2, 1938. The electrocardiograms show QRS changes of both the anterior and posterior wall types. Record A shows a concordant elevation of the S-T segment in the limb leads; C shows a concordant T-wave inversion in the limb leads. For discussion, see text.

Of twenty-six cases in which there was T-wave inversion in the limb leads, this change occurred within two weeks after the attack in fifteen (within five days in six), and after two weeks in four. In the remaining seven cases, the time of the T-wave inversion could not be determined exactly.

TABLE II

<i>1. Anterior wall type of myocardial infarction</i>	
A—S-T stage	B—T stage
(a) Elevation of S-T in all limb leads, or absence of S-T depression in Lead III, with marked elevation in Leads I and II	(a) T inverted and coronary in type in all limb leads
(b) Deep Q_1 present and/or QRS directed entirely downward in CF_2 and/or CF_4 , or a deeply inverted first phase present in these chest leads	(b) ditto S-T stage
8 cases included, friction rub in 4, autopsy in 2 (cf. Figs. 1, 2)	7 cases included, friction rub in 2, autopsy in 0 (cf. Fig. 3)
<i>2. Posterior wall type of myocardial infarction</i>	
A—S-T stage	B—T stage
(a) Elevation of S-T in all limb leads, or absence of S-T depression in Lead I, with marked elevation in Leads II and III	(a) T inverted and coronary in type in all limb leads
(b) $a Q_3$ (and Q_2) present 8 cases included, friction rub in 3, autopsy in 0 (cf. Fig. 4)	(b) ditto S-T stage 7 cases included, friction rub in 2, autopsy in 0 (cf. Fig. 4)
<i>3. Combined anterior and posterior wall type of myocardial infarction</i>	
A—S-T stage	B—T stage
(a) Elevation of S-T in all limb leads, or absence of S-T depression in Lead III (or I), with marked elevation in Lead I (or III)	(a) T inverted and coronary in type in all limb leads
(b) Q_3 (and Q_2) present, and QRS in CF_2 and/or CF_4 directed entirely downward or a deeply inverted first phase, and/or a deep Q_1 present	(b) ditto S-T stage
6 cases included, friction rub in 1, autopsy in 1 (cf. Fig. 5)	9 cases included, friction rub in 2, autopsy in 2 (cf. Fig. 5)
<i>4. Atypical pattern of myocardial infarction</i>	
A—S-T stage	B—T stage
(a) Elevation of S-T in all limb leads, or absence of depression in Lead III (or I), with marked elevation in Lead I (or III)	(a) T inverted and coronary in type in all limb leads
(b) No special QRS pattern in limb or chest leads	(b) ditto S-T stage
(c) Evolution showing discordant changes in S-T-T in Leads I and III pointing to an anterior or posterior wall type	(c) ditto S-T stage
3 cases included, friction rub in 0, autopsy in 0 (cf. Fig. 6)	3 cases included, friction rub in 0, autopsy in 0 (cf. Figs. 6, 7)

THE RELATION OF A PERICARDIAL FRICTION RUB TO THE PRESENCE OF DIFFUSE PERICARDITIS COMPLICATING ACUTE MYOCARDIAL INFARCTION

A pericardial friction rub was heard in 11 of these 39 cases (Table I). The absence of a friction rub cannot rule out diffuse pericarditis, for in one of the two autopsy cases of diffuse pericarditis reported here no

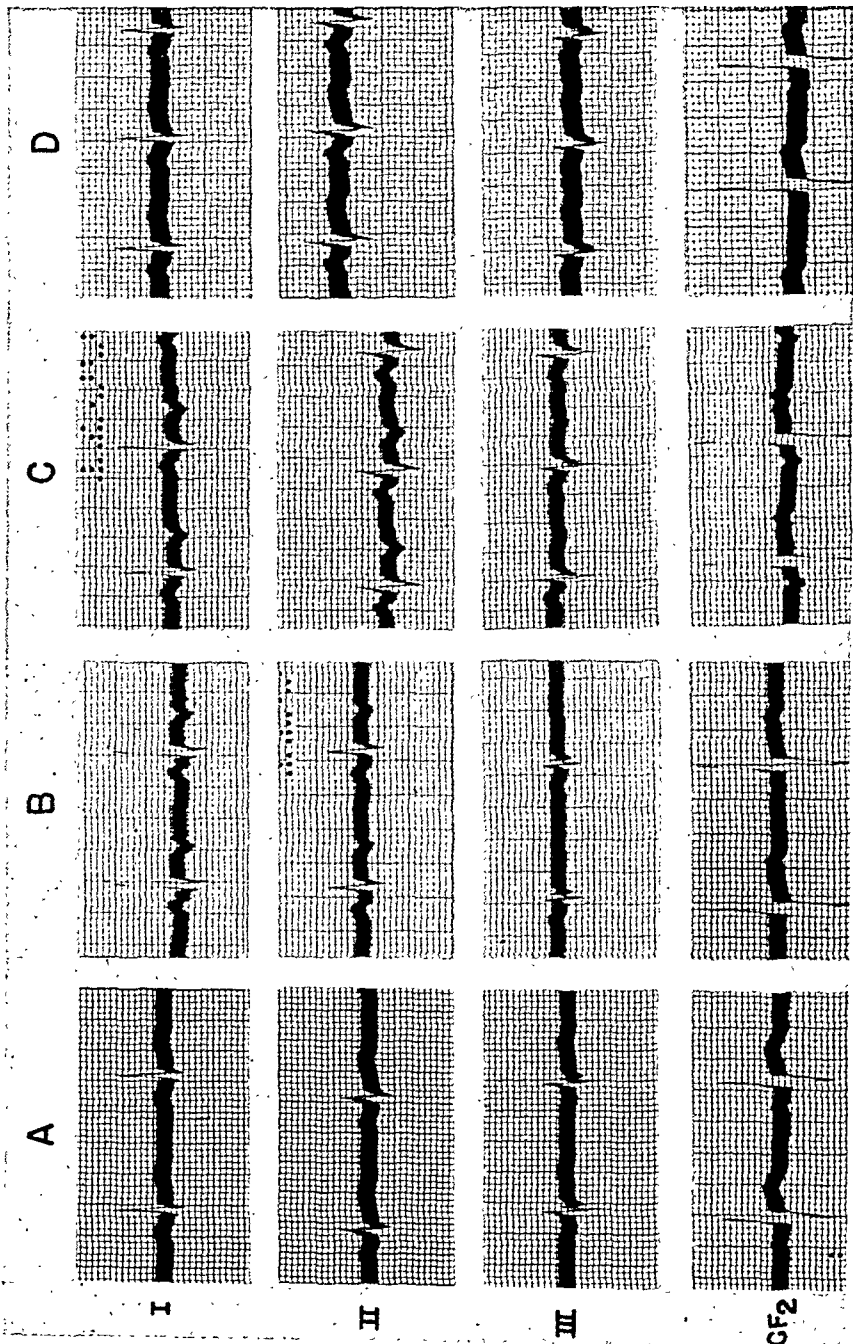


Fig. 6.—(Case 36.) The patient had the attack on November 22, 1937. Record A was taken on November 22, 1937. Record B on November 26, 1937, C on December 6, 1937, D on February 26, 1938. There are concordant S-T and T changes in the limb leads. Note the T-wave inversion which occurred five days after the attack, when S-T was still elevated. Discussed in text.

friction rub was detected, and it was not heard in two of four cases reported by Saphir, Priest, Hamburger, and Katz.⁶ On the other hand, not every patient with myocardial infarction and an audible friction

rub can be expected to show signs of diffuse pericarditis. Thus, with an anterior wall infarct the friction rub may be evidence only of a local pericarditis superimposed on the infarcted area. An audible pericardial rub in a case of posterior wall infarction is more likely to be a sign of diffuse pericarditis. It is quite possible that the friction rub will be heard more often with more frequent observations and more careful auscultation.

S-T-T CHANGES IN THE CHEST LEADS

Since diffuse pericarditis, of itself, usually produces S-T elevation in the chest leads (Holzmann,¹¹ Winternitz and Langendorf,² Bellet and McMillan,¹² Vander Veer and Norris¹³), it would tend to exaggerate the S-T elevation in cases of anterior infarction and to reduce the S-T depression in cases of posterior wall infarction. Similarly, the tendency towards T-wave inversion in the chest leads as a later result of diffuse pericarditis would be expected to counteract, to some extent, the evolution of an upright coronary T wave in posterior wall infarction and to exaggerate the T-wave inversion in the anterior type.

Chest leads were available in thirty-three of our thirty-nine cases. In twenty-five cases CF_2 was taken, and in eight cases, both CF_2 and CF_4 were recorded. In group 1, all of the electrocardiograms, except one with an upright, pointed T wave in CF_2 , were in accord with the expected pattern of the anterior wall type. Similarly, in group 2 all except one, which showed an inverted T in CF_4 (Fig. 4), were in accord with the expected posterior wall type. In group 3, in which the S-T-T configuration was unpredictable because it was the resultant of opposite tendencies due to simultaneous anterior and posterior wall infarction, the S-T-T of the chest leads was typical of anterior infarction in six cases, and of posterior infarction in one case. In group 4 the S-T-T of the chest leads was in accord with the type of infarction which was indicated by the transient, discordant S-T-T changes in the limb leads.

A discussion of the significance of these changes can best be deferred until those in the limb leads have been considered.

THE RELATION OF THE SPECIAL ELECTROCARDIOGRAPHIC PATTERN TO DIFFUSE PERICARDITIS COMPLICATING RECENT MYOCARDIAL INFARCTION

It is known that although uncomplicated, diffuse pericarditis often produces the typical concordant S-T-T changes, it occurs sometimes without characteristic changes. The absence of electrocardiographic changes, therefore, does not exclude pericarditis. This is true also of diffuse pericarditis complicating recent myocardial infarction. Examination of nineteen autopsy cases with electrocardiographic correlation, as reported in the literature and listed in Table III, reveals only eight in which the pattern selected and illustrated in the present report appears.

TABLE III

ELECTROCARDIOGRAPHIC OBSERVATIONS IN 19 CASES OF RECENT MYOCARDIAL INFARCTION ASSOCIATED WITH DIFFUSE PERICARDITIS (DIAGNOSIS CONFIRMED AT AUTOPSY)

AUTHOR	CASE	S-T STAGE	T STAGE	LOCATION OF INFARCT
Barnes ¹	1	concordant	discordant	Anterior wall of left ventricle, apex
Bohning and Katz ⁷	1C*	absence of discordance	-	Septum, anterior wall and apex of left ventricle
	2B†	-	discordant	Anterior wall of left ventricle
	4A	discordant	-	Posterior wall of left ventricle
Büchner, Weber, and Haager ⁹	1	absence of discordance	-	Anterior wall of left ventricle, anterior septum, apex
	9	-	discordant	Anterior and posterior wall of left ventricle, apex
Jervell ⁸	17	-	discordant	Anterior and posterior wall of left ventricle
	37	discordant	-	Posterior wall, septum
	42	concordant	discord.?	Posterior wall of left ventricle
	55	discordant	-	Posterior wall of left ventricle
	56	discordant	concord.?	Anterior and posterior wall of left ventricle
Saphir, Priest, Hamburger, and Katz ⁶	3	discordant	-	Lateral wall of left ventricle
	7	-	discordant	Lateral wall of left ventricle
	9	-	discordant	Anterior wall of left ventricle
	26	-	discordant	Anterior wall of left ventricle
Winternitz and Langendorf ²	71	concordant	discordant	Posterior wall of left ventricle
	72	absence of discordance	-	Anterior and posterior wall of left ventricle
	74	discordant	-	Anterior wall of left ventricle, apex
	76	concordant	-	Lateral wall of left ventricle

*Case 2 of the present report.

†Case 1 of the present report, included because of a concordant S-T stage.

It seems significant that in all of these eight cases there were concordant changes in the S-T stage and none in the T stage. It is also significant that Weinberg and Katz' series¹⁰ of autopsy cases of myocardial infarction with concordant changes in the T stage contains no cases of anterior or posterior infarction complicated by diffuse pericarditis. In the two autopsy cases with T-wave inversion in all limb leads which are included in their report there were multiple infarcts, but no diffuse pericarditis. Therefore, we hesitate to ascribe the concordant T-wave inversion in the cases of group 1 and 2 to the effect of complicating diffuse pericarditis and are more inclined to consider that pattern, described as "T_N type" by Weinberg and Katz,¹⁰ together with a QRS pattern in the limb and chest leads of either of the two classical types, as reflecting extensive myocardial infarction, involving both the anterior and posterior walls.

The absence of electrocardiographic evidence in autopsy cases of recent infarction associated with diffuse pericarditis does not preclude the possibility that the presence of definite electrocardiographic changes can be taken as presumptive evidence of diffuse pericarditis. An analysis of the data assembled in this report, when coordinated with the study of autopsy material, as reported here and previously, suggests the following conclusions:

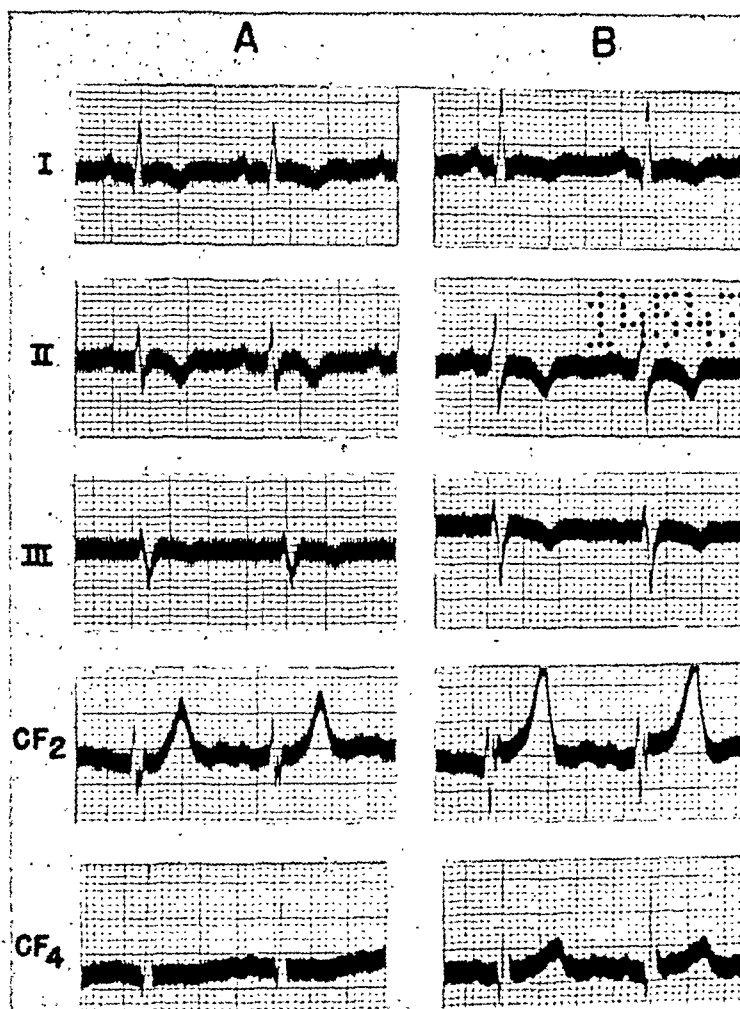


Fig. 7.—(Case 39.) The patient had the attack on April 5, 1939. Record A was taken on May 5, 1939. B on July 1, 1939. The QRS does not fit any myocardial infarction pattern. There is a concordant T-wave inversion in the limb leads. Note upright T in the chest leads, pointing to infarction of the posterior wall. Discussed in text.

1. A transient, concordant S-T stage in the limb leads in an otherwise discordant S-T-T evolution, with the QRS pattern of anterior or posterior wall infarction (groups 1 and 2), is highly suggestive of accompanying diffuse pericarditis.

2. A concordant T-wave stage in the limb leads is suggestive of extensive infarction, especially when this pattern develops within a week, while the elevation of the S-T segment is still present. However, further anatomic correlation studies are necessary to evaluate the role of diffuse pericarditis in producing the pattern of concordant T-wave inversion in simple infarction.

3. In the presence of the QRS changes of both anterior and posterior infarction in the limb and chest leads, and of concordant S-T-T changes in the limb leads (group 3), no statement can be made as to the presence or absence of diffuse pericarditis.

4. In the absence of any QRS pattern of infarction in the limb and chest leads, and with the presence of concordant S-T-T changes in the limb leads (group 4), the evolution of a tall, upright T wave in the chest leads indicates infarction and differentiates the record from one of uncomplicated diffuse pericarditis.

As a result of these deductions, the number of cases in which it can be presumed that there is a complicating diffuse pericarditis is more limited. If the ten cases of group 3 are discounted, since the involvement of both the anterior and posterior walls may account for the concordant S-T-T changes in the limb leads, there remain twenty-nine of the original series of thirty-nine cases with an electrocardiographic pattern of infarction which possibly reflects a complicating diffuse pericarditis. In seventeen of these twenty-nine cases there was a concordant T stage, and this, judging from the post-mortem evidence, may be assumed to be the result of extensive myocardial infarction. This is particularly true of the three cases with the unexpected T-wave inversion which occurred within five days after the attack, for pericarditis, per se, does not lead to T-wave inversion until weeks after the early S-T stage (Winternitz and Langendorf²). Thus, after careful analysis, in only twelve (3.2 per cent) of the series of 380 cases of recent myocardial infarction can an electrocardiographic diagnosis of simple infarction associated with diffuse pericarditis be justified. Since the diagnosis is based mainly on a transient change during the S-T stage of the electrocardiographic evolution caused by the infarction, it seems likely that many cases may have been missed because no records were taken at the time when this change was present. The greater statistical frequency of complicating diffuse pericarditis at autopsy would bear this out. The electrocardiographic diagnosis of diffuse pericarditis complicating recent myocardial infarction will be made with greater frequency only when electrocardiograms are made more often during the S-T stage of infarction.

SUMMARY AND CONCLUSIONS

1. Out of 380 consecutive cases of recent myocardial infarction, thirty-nine presented a limb lead pattern of concordant S-T elevation or concordant T-wave inversion which fulfilled the criteria for the diagnosis of complicating pericarditis as formulated by Barnes.

2. Both QRS and S-T-T changes in the limb and chest leads have to be taken into account and studied in their relation to each other, if uncomplicated diffuse pericarditis is to be differentiated electrocardiographically from myocardial infarction and from myocardial infarction complicated by diffuse pericarditis.

3. Autopsy control in four cases of the present report, post-mortem correlation in previous reports of cases of recent myocardial infarction with diffuse pericarditis, autopsy observations in cases of infarction with the "T_x type" of electrocardiogram, and electrocardiographic correlation in autopsy cases of recent myocardial infarction with diffuse pericarditis lead to the following conclusions:

(a) A transient, concordant S-T elevation in the limb leads in an otherwise discordant S-T-T evolution in cases of anterior or posterior wall infarction is highly suggestive of a complicating diffuse pericarditis.

(b) A concordant T-wave inversion in the limb leads, with QRS changes in the limb and chest leads of either the anterior or posterior wall type, is caused by extensive myocardial infarction, and cannot be considered a result of simple infarction complicated by diffuse pericarditis. However, further anatomic correlation studies are necessary to substantiate this statement.

4. As a result of these deductions, in only twelve (3.2 per cent) of the present series of 380 cases of recent myocardial infarction could a diagnosis of complicating diffuse pericarditis be made. Serial electrocardiograms during the S-T stage of infarction should make the percentage of electrocardiographic diagnoses of complicating diffuse pericarditis more nearly approach the post-mortem incidence (15.3%).

I am deeply indebted to Dr. L. N. Katz for his advice and criticism in the preparation of this report.

REFERENCES

1. Barnes, A. R.: Electrocardiographic Pattern Observed Following Acute Coronary Occlusion Complicated by Pericarditis, *AM. HEART J.* 9: 734, 1934.
2. Winternitz, M., and Langendorf, R.: Das Elektrokardiogramm der Perikarditis, *Acta med. Scand.* 94: 141 and 274, 1938.
3. Barnes, A. R., and Mann, F. C.: Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, *AM. HEART J.* 7: 477, 1932.
4. Burchell, H. B., Barnes, A. R., and Mann, F. C.: The Electrocardiographic Picture of Experimental Localized Pericarditis, *AM. HEART J.* 18: 133, 1939.
5. Stewart, C. F., and Turner, K. B.: A Note on Pericardial Involvement in Coronary Thrombosis, *AM. HEART J.* 15: 232, 1938.
6. Saphir, O., Priest, W. S., Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis and the Resulting Myocardial Changes, *AM. HEART J.* 10: 567, 1935.
7. Bohning, A., and Katz, L. N.: Four Lead Electrocardiogram in Cases of Recent Coronary Occlusion, *Arch. Int. Med.* 61: 241, 1938.
8. Jervell, A.: Elektrokardiographische Befunde bei Herzinfarkt, *Acta med. Scand. Sup.* 68, 1935.
9. Büchner, F., Weber, A., and Haager, B.: Koronarinfarkt und Koronarinsuffizienz, Leipzig, 1935, G. Thieme.
10. Weinberg, H. B., and Katz, L. N.: A Common Electrocardiographic Variant Following Acute Myocardial Infarction. The T_x Type, *AM. HEART J.* 21: 699, 1941.
11. Holzmann, M.: Klinische Erfahrungen mit elektrokardiographischen Brustwandableitungen, *Arch. f. Kreislaufforsch.* 1: 1, 1937.
12. Bellet, S., and McMillan, T. M.: Electrocardiographic Patterns in Acute Pericarditis. Evolution, Causes and Diagnostic Significance of Patterns in Limb and Chest Leads; a Study of Fifty-Seven Cases, *Arch. Int. Med.* 61: 381, 1938.
13. Vander Veer, J. B., and Norris, R. F.: The Electrocardiographic Changes in Acute Pericarditis, *J. A. M. A.* 113: 1483, 1939.

THE FREQUENCY OF ELECTROCARDIOGRAPHIC VARIATIONS IN NORMAL, UNANESTHETIZED DOGS

JOSEPH LALICH,* M.D., LOUIS COHEN, A.M., AND GEORGE WALKER, M.D.
KANSAS CITY, KAN.

THE observation that T waves not infrequently may be inverted in all three leads in normal dogs was first made by Smith.¹ Attention was directed to the extreme variability in the T waves of normal dogs, as contrasted to the T waves of normal human subjects, by Barnes and Mann,² who concluded that, unless the direction of the T wave had been established under normal conditions in dogs, conclusions drawn following ligation of the coronary arteries might prove confusing. Katz, Soskin, and Frisch³ studied serial electrocardiograms in normal, unanesthetized dogs over periods of four months and concluded that the variability in the T waves was caused by the relative mobility of the dog's heart. These authors suggested that, previous to experimental electrocardiographic studies on dogs, serial records over a period of days were indicated. Harris and Hussey⁴ reported on the frequency and direction of T-wave variations in seventy-five records on fifty normal dogs. Gross and Calef⁵ found that their normal records showed the T-wave variations which had been reported by the previous workers.

Numerous statements have been made in the literature to the effect that electrocardiograms taken on dogs differ in some respects from human records, and that electrocardiograms which are considered pathologic in man may be observed fairly frequently under normal circumstances in the dog. Since the dog continues to be the most frequently used animal in experimental electrocardiography, data on the variation of individual complexes in normal dogs are of sufficient importance to be enlarged upon. We believe that a further addition to our knowledge of T, Q, and S wave variations in normal dogs, as to their frequency and some other minor changes not mentioned previously, is needed.

METHOD

Healthy, adult dogs were trained to lie on either their right or left side, so that they were relaxed and flat on the table while the record was being taken. Animals which could not be trained to relax on the table were not used in this study. On five dogs records were made while they lay first on one side, and then on the other, in order to ascertain the effect of change of position on the electrocardiogram. From two to seventeen records were taken on each animal within four weeks' time. The records were standardized so that one millivolt produced a deflection of one centimeter.

From the Hixon Laboratory for Medical Research, Departments of Medicine and Pathology, University of Kansas.

*George A. Breon Fellow in Experimental Medicine.

Received for publication Sept. 9, 1940.

RESULTS

The data have been arranged in tabular form so that the variations and the frequency with which they occurred might be observed in each animal. A total of 218 records on twenty-four normal dogs were obtained.

Occurrence of Variations in the Various Complexes (Table I).—P waves are almost always present in normal dogs. A variation in the amplitude of the P wave in any one lead was usually associated with sinus arrhythmia. This occurred in sixteen instances in Lead II, and 12 times in Lead III. Whenever a change in the amplitude or direction of the P wave occurred, the animal was usually apprehensive or excited. P-wave inversion was observed in Leads I and III, but never in Lead II.

Study of the Q waves and inverted T waves in all three leads revealed that when there was a Q wave in Lead I the T wave in that lead was likely to be inverted. This was not the case in Leads II and III. The amplitude of the Q wave was found to be important, because whenever it was greater than 4 mm. the following T wave was inverted in over 90 per cent of the cases, and this was true of all three leads. This relationship between deep Q waves and inverted T waves was especially apparent in Lead I; when T shifted from an inverted position to an upright one, the Q wave would either disappear or become very small. The Q waves were deepest and most frequently found in Lead II.

The data reveal an interesting relationship between the presence of S waves and upright T waves. S waves were least frequent in Lead I, as were upright T waves. In Leads II and III the S waves were more frequent, and so were upright T waves. In Lead III, in which S waves occurred most frequently, upright T waves were most common. Just as a Q wave is likely to be followed by an inverted T wave, so, when an S wave is present, upright T waves will usually be found in any lead, especially Lead III. S waves were usually deepest and most frequently encountered in Lead III. The relationship between upright T waves and deep S waves in Lead III does not appear to be a close one, because S_3 is not as likely to change as Q_1 when there is a reversal in the direction of the T wave in these leads.

Contrary to a prevalent idea, as was first pointed out by Harris and Hussey, inverted T waves preponderate in Lead I, whereas upright T waves are the most frequent in Lead III. Although there is apparently a reciprocal relationship between T_1 and T_3 , it is not necessarily true that an inverted T_1 will be accompanied by an upright T_3 , or vice versa.

Minor RS-T deviations, seldom exceeding 1 mm., were found most frequently in Lead II. No correlation could be established between RS-T deviation and inverted or upright T waves.

Further Analysis of the Data in Table I.—Reversal in the direction of the T wave occurred in nineteen out of twenty-four dogs. These reversals were more frequent in Leads I and II. Inversion of the T wave

in all three leads was less frequent; it was observed in seven out of the 24 dogs in our series. Applying Pardee's criteria to Q_3 , we found that Q_3 exceeded 25 per cent of the tallest R wave in nine records. Deep S waves were larger than 25 per cent of the tallest R wave in ten records.

Since Q and S waves were found to be related to T waves, it was considered important to analyze the data for the occurrence of Q and S waves in the same lead. It was found that the two occurred least frequently together in Lead I and most frequently in Lead III. In those instances in which both were present in Leads I and III, usually either the Q or the S wave measured one millimeter or less. In Lead II, however, it was not uncommon to find both Q and S waves which measured more than two millimeters.

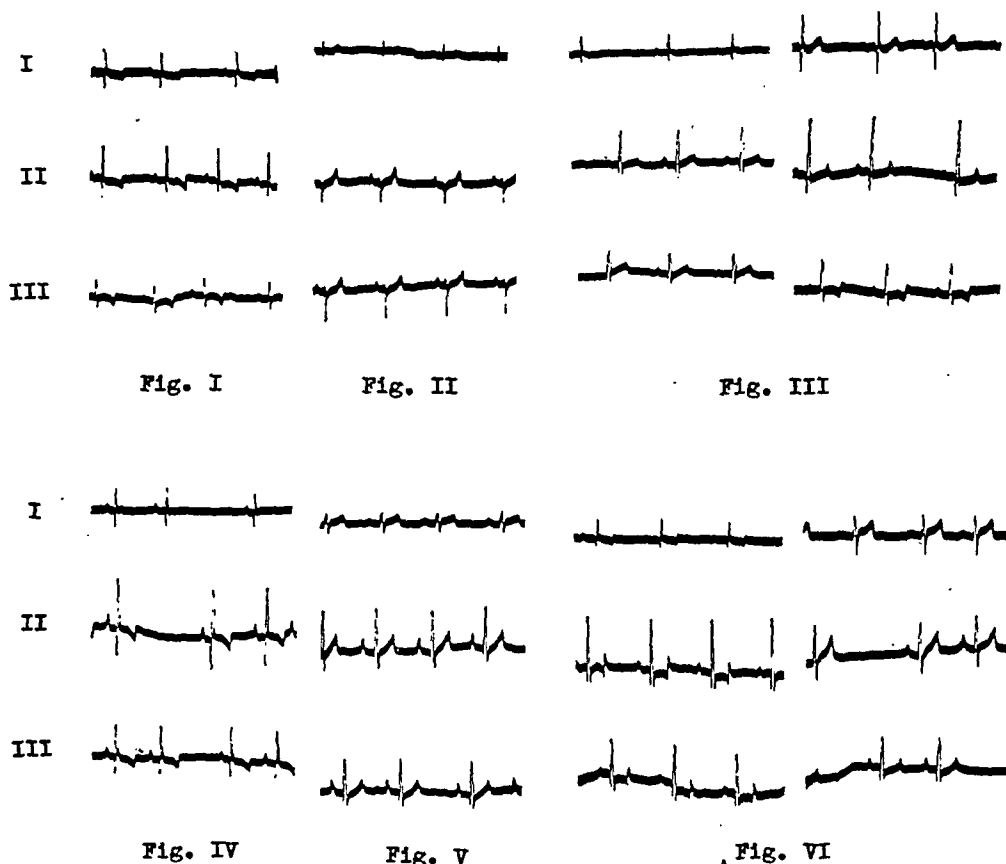


Fig.—I, Note inverted T waves in all three leads, also Q_1 and Q_2 . II, An example of marked left axis deviation in a presumably normal dog. III, Tracings from the same animal on different days. Note deepening of Q_1 and increased amplitude of T_1 ; this is rare; such a deep Q is usually associated with an inverted T (Compare with IV). Observe deepening of S_2 and reversal of T_2 in the second record. This combination is also unusual. IV, Note association of a deep Q with an inverted T in Leads II and III. This is usual when Q is present and equal to 25 per cent or more of the tallest R. V, S_2 is more than 25 per cent of tallest R. Note that all T waves are upright, which is common when a large S is present in any lead, though not invariable. VI, Tracings from the same animal on different days. Note reversal of T_1 , disappearance of Q_1 , and appearance of a deep S_1 in the second record. Note RS-T depression in the record for the first day, Leads I and II.

The electrical axes were determined by Dieuaide's method⁶ in ten dogs which had ten or more records taken. Out of each group of records three

TABLE I

DOG NUMBER		NUMBER OF RECORDS TAKEN	P WAVES			Q WAVES			S WAVES			T WAVES						RS-T																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
			L ₁	L ₂	L ₃	L ₁	L ₂	L ₃	L ₁	L ₂	L ₃	L ₁			L ₂			L ₃																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																						
												↓	↑	↔	↓	↑	↔	↓	↑	↔																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																				
1867		10	10	10	10	9	10	9	0	0	0	8	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

TABLE II

DOG NUMBER	NUMBER OF RECORDS STUDIED	REVERSAL IN DIRECTION OF T WAVES			INVERTED T WAVES, ALL LEADS	Q ₃ EXCEEDS 25% TALL- EST R COMPLEX	S ₂ EXCEEDS 25% ALL R COMPLEXES	PRESENCE OF Q AND S COMPLEXES AT SAME TIME		
		L ₁	L ₂	L ₃				L ₁	L ₂	L ₃
1867	10	3	3	0	0	0	0	0	0	0
L.F.	11	3	1	0	0	1	0	0	1	0
L.3	9	1	0	0	0	0	0	0	0	3
L.1	10	1	0	0	0	0	0	0	5	0
1887	10	3	3	2	2	0	0	0	11	10
1885	10	1	2	3	5	6	0	3	1	3
1880	16	0	0	0	15	0	0	10	16	14
1889	10	1	0	0	0	0	3	0	0	0
June P.	12	2	0	0	0	0	0	0	6	11
F.B.	3	0	0	0	0	0	0	0	0	3
C.A.	13	3	0	0	0	0	1	0	0	3
1866	11	2	3	1	0	0	1	0	8	6
1882	2	0	1	1	0	0	0	0	1	1
1881	3	0	0	0	0	0	0	0	2	1
1886	5	2	2	0	0	0	1	0	2	2
1888	3	0	0	0	0	0	1	0	2	2
F.W.	3	2	0	0	1	0	0	0	0	2
1863	17	0	2	0	0	0	0	1	3	15
1873	17	1	3	4	0	0	0	2	9	6
1864	10	5	2	3	4	0	0	0	0	0
1865	10	6	2	0	0	0	0	0	5	6
L.H.C.	8	1	0	1	0	0	0	0	4	4
Whitey	8	3	1	1	1	0	0	0	4	2
Blackie	7	2	2	0	0	0	1	0	2	3
Total	218	42	27	17	28	9	10	16	82	97

The third column of figures (reversal in direction of T waves) records how many times an upright T wave became inverted, or vice versa, in the series of records from the animal identified in column one. The other column headings are self-explanatory.

which showed the greatest degree of variation were chosen. The greatest variation observed in any one animal was 75 degrees; the axis shifted from minus 65 degrees to plus 10 degrees. Over 60 per cent of the recorded axes fell between 50 degrees and 75 degrees. The usual shift in axis from day to day in the majority of the animals was less than 15 degrees.

We found no consistent correlation between electrocardiographic variations and the side the animal was lying on. T-wave reversals did not necessarily follow changes in the electrical axis.

One animal, dog 89, consistently had an electrocardiogram unlike those of the other animals. As this animal's electrocardiogram was so constantly different in over twenty-five records, we are publishing it as an example of marked left axis deviation in a normal dog.

SUMMARY

Two hundred eighteen electrocardiograms were made on twenty-four normal dogs.

Under normal conditions the P waves showed changes in direction and amplitude in the same lead. Since these changes happened more frequently in nervous or excited animals with sinus arrhythmia, we suggest that they may be associated with vagal or sympathetic nervous influences. Changes in amplitude and reversal of direction of the T waves are tabulated to illustrate the variability in this complex which has been reported previously. A change in the amplitude or disappearance of Q and S waves is the next most frequent variation in the electrocardiograms of normal dogs. Even though variations do occur in the various complexes in different animals, each dog's records are characteristic for that animal. Slight RS-T deviations from the isoelectric line occurred, but seldom exceeded one millimeter. There was a relationship between Q waves and inverted T waves in Lead I which was observed in 78 per cent of the records in our series. Likewise, there was a relationship between S waves and upright T waves in Lead III; this was observed in 75 per cent of the records. Apparently, therefore, there is a reciprocal relation between Q waves and inverted T waves in Lead I, and between S waves and upright T waves in Lead III.

Extrasystoles occurred only once in this series of trained animals, and "dropped ventricular beats" were observed in less than 2 per cent of the records.

We wish to thank Dr. R. H. Major for his help, suggestions, and criticisms.

REFERENCES

1. Smith, F. M.: Ligation of Coronary Arteries With Electrocardiographic Study, *Arch. Int. Med.* 22: 81, 1918.
2. Barnes, A. R., and Mann, F. C.: Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, *AM. HEART J.* 7: 477, 1931.

3. Katz, L. N., Soskin, S., and Frisch, R.: Variations in Contour of the Records Found in Serial Electrocardiogram of the Dog, *Proc. Soc. Exper. Biol. & Med.* 32: 208, 1934.
4. Harris, B. R., and Hussey, R.: The Electrocardiographic Changes Following Coronary Artery Ligation in Dogs, *AM. HEART J.* 12: 724, 1936.
5. Gross, L., and Calef, B.: Electrocardiographic Changes in Dog Following Sudden Occlusion of the Anterior Descending Branch Under Various Experimental Conditions, *AM. HEART J.* 14: 677, 1937.
6. Ashman, R., and Hull, E.: *Essentials of Electrocardiography*, Macmillan, 1940.

THE INCIDENCE OF RHEUMATIC AND CONGENITAL HEART DISEASE AMONG SCHOOL CHILDREN OF LOUISVILLE, KY.

MORRIS M. WEISS, M.D.
LOUISVILLE, KY.

THE variation in the geographic distribution of rheumatic heart disease among the school children of the United States has been emphasized by numerous observers. All are in accord that the disease is much less frequent in the South than in the North. Paul and Dixon,¹ in a survey of rheumatic heart disease among American Indian school children in Southern and Northern reservations, found an incidence of 0.5 per cent in the former, and 4.5 per cent in the latter, group. This study has especial significance because both surveys were made by the same examiners. Sampson, Christie, and Geiger,² of San Francisco, have reviewed the literature on the incidence of rheumatic heart disease in the school populations of the middle, western, and eastern United States; they stressed the marked geographic differences of the disease, and found that San Francisco school children showed the lowest incidence, i.e., 0.22 per cent. In a more recent survey, Rauh³ found in Cincinnati an incidence similar to that in San Francisco. Of 85,389 school children, 0.2 per cent had rheumatic heart disease. Statistics on the geographic distribution of congenital heart disease are not as reliable because the majority of the surveys assumed that 20 per cent of organic heart disease in children is congenital. This is a false assumption.

The present report is a study of the incidence of rheumatic and congenital heart disease in the school children of Louisville.

Louisville, situated on a plateau about 60 feet above the Ohio River at an ordinary stage of water, is in latitude 38° 15' N, and longitude 85° 45' W. It is 449 feet above sea level. The terrain is undulating, with good drainage. The 1930 census showed a population of 307,745 in an area of 37.88 square miles. The population is composed of 251,364 native whites, 8,938 foreign-born whites, and 47,354 negroes. The mean annual temperature is 63.1° F., the mean annual maximum, 78.5° F., and the mean annual minimum, 34.5° F. The mean relative humidity is 76 per cent in the morning and 62 per cent in the afternoon. There is an average of 124 days of rainfall, with an average annual precipitation of 43.49 inches. The average annual snow precipitation is 29 inches. Clear days number 128, cloudy days, 109 and partly cloudy, 128.

From the Department of Health, City of Louisville.
Received for publication Sept. 14, 1940.

METHOD OF STUDY

The school physicians connected with the Department of Health of the City of Louisville each year examine all the pupils who attend the kindergarten, first, fourth, and seventh grades, and the first year of the junior high school. Therefore, all the children in the entire school system are examined at least once in three years. Examinations are made with the chest exposed. The school physicians do not attempt to make an etiologic classification of the cardiac abnormalities which they find. Under the heading of "heart" on the child's health card, a notation is made as to any deviation from the presumed normal, and the child is then referred to the family physician for further examination. For three consecutive school years, from 1936 through 1939, all children designated "heart" in each school, public and parochial, were re-examined by myself. Children who were receiving bedside instruction because of home confinement as a result of heart disease were checked through the Board of Education. The cases of pupils who died in the public hospitals during the years of the survey were included in the total number analyzed. The criteria for the diagnosis of rheumatic and congenital heart disease, as specified by Paul and his associates,⁴ were followed, except that apical systolic murmurs were ignored unless they were accompanied by cardiac enlargement, or were very loud and heard over a wide area of the precordium. In borderline cases the children were re-examined several times during the three years of the study. Roentgenologic and electrocardiographic facilities were rarely available.

A yearly average of 41,905 children from 6 through 14 years of age attended the public and parochial schools from 1936 through 1939. A total of 221, or 0.52 per cent, had rheumatic or congenital heart disease (Table I). There were 35,713 white children, of which number 196, or 0.54 per cent, had these etiologic types of heart disease. Of 6,192 negro children, 25, or 0.45 per cent, had rheumatic or congenital lesions. Rheumatic heart disease was present in 153, or 0.36 per cent, and congenital defects in 68, or 0.16 per cent. Thus, rheumatic heart disease accounted for 69 per cent of the 221 cases of organic heart involvement. Of the 153 cases of rheumatic heart disease, 131 occurred in white children. This is an incidence of 0.33 per cent. The incidence in negro children was the same, 0.35 per cent (twenty-two cases). The incidence of congenital heart disease was greater among the white than among the colored children. Only three, or 0.05 per cent, of the negro children had congenital lesions, in contrast to sixty-five, or 0.18 per cent, in the white pupils.

Rheumatic heart disease was approximately equally common in both sexes of both races (Table II). Rheumatic valve lesions were present in sixty-six white boys, sixty-five white girls, twelve negro boys, and ten negro girls. Congenital heart disease was found in twenty-six

TABLE I

DISTRIBUTION AS TO RACE OF RHEUMATIC AND CONGENITAL HEART DISEASE AMONG
41,905 SCHOOL CHILDREN

RACE	NUMBER OF CHILDREN	RHEUMATIC		CONGENITAL		TOTAL NUMBER	
		NO.	%	NO.	%	ORGANIC HT. DIS. NO. .	%
White	35,713	131	0.33	65	0.18	196	0.54
Negro	6,192	22	0.35	3	0.05	25	0.45
Total	41,905	153	0.36	68	0.16	221	0.52

white boys, thirty-nine white girls, three negro boys, and no negro girls. The sex distribution of all the school children was approximately equal in both races.

TABLE II

DISTRIBUTION AS TO RACE, AGE, AND SEX OF RHEUMATIC AND
CONGENITAL HEART DISEASE

AGE	RHEUMATIC (153 CASES)						CONGENITAL (68 CASES)					
	WHITE			NEGRO			WHITE			NEGRO		
	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL
6- 7	1	4	5	1	0	1	8	12	20	0	0	0
7- 8	1	1	2	1	0	1	5	5	10	1	0	1
8- 9	4	5	9	1	0	1	3	2	5	0	0	0
9-10	2	6	8	1	0	1	2	1	3	1	0	1
10-11	3	7	10	2	2	4	2	2	4	0	0	0
11-12	6	6	12	4	3	7	1	3	4	0	0	0
12-13	12	8	20	0	1	1	1	3	4	0	0	0
13-14	10	8	18	0	0	0	2	3	5	0	0	0
14-15	27	20	47	2	4	6	2	8	10	1	0	1
Total	66	65	131	12	10	22	26	39	65	3	0	3

An attempt was made to ascertain the social distribution of the rheumatic cases. Despite overlapping of economic levels in many of the schools, there was a greater incidence of rheumatic heart disease among the children from the "poorer" districts than from the "better" districts of the city. However, the incidence was not significantly higher in the recent slum clearance areas of the city.

DISCUSSION

The incidence of rheumatic heart disease in Louisville school children is similar to that in San Francisco² and Cincinnati.³ The fact that 69 per cent of the cases of organic heart disease were rheumatic confirms the observations made in those communities that the incidence of rheumatic heart disease in children cannot be ascertained on the assumption that 80 per cent of the murmurs in children are of rheumatic origin.

There is a divergence in the reports as to the racial incidence of rheumatic heart disease. Rauh³ found that the incidence of acquired heart disease was almost twice as high among colored as among white children. Others^{5, 6} have reported a higher incidence in white children. This study did not reveal any racial difference in incidence.

No attempt was made to make a careful anatomic diagnosis of the lesions encountered, but it is of interest that there was only one case of dextrocardia and not a single instance of complete heart block.

No cases of rheumatic or congenital disease were encountered in siblings.

The fact that the incidence of rheumatic heart disease was not significantly higher in the slum clearance areas of the city would indicate, as others have noted, that rheumatic fever is not strictly a disease of paupers.

SUMMARY

1. A study is presented of the incidence of rheumatic and congenital heart disease among 41,905 school children from 6 through 14 years of age who yearly attend the schools of Louisville, Ky.

2. A total of 221, or 0.52 per cent, had rheumatic or congenital heart lesions; this included 0.54 per cent of the white and 0.45 per cent of the negro children.

3. Rheumatic heart disease accounted for 69 per cent of the 221 cases.

4. Rheumatic heart disease occurred in 0.33 per cent of the white and 0.35 per cent of the negro pupils.

5. Congenital heart lesions were found in 0.18 per cent of the white and 0.05 per cent of the negro children.

6. Rheumatic valve lesions were approximately equally common in both sexes of both races. No cases were encountered in siblings.

7. Although the incidence was not higher in the slum clearance areas of the city, there was a greater incidence of rheumatic lesions in children from the "poorer" than from the "better" districts.

I am indebted to Dr. H. R. Leavell, Director of the Department of Health, Miss Florence Hauswald, Superintendent of Public Health Nurses of the City Health Department, and Miss Mary M. Wyman, Director of the Department of Health and Safety Education, Louisville Public Schools, for their assistance and cooperation in this study.

REFERENCES

1. Paul, J. R., and Dixon, G. L.: Climate and Rheumatic Heart Disease. A Survey Among American Indian School Children in Northern and Southern Localities, *J. A. M. A.* 108: 2096, 1937.
2. Sampson, J. J., Christie, A., and Geiger, J. C.: Incidence and Type of Heart Disease in San Francisco School Children, *AM. HEART J.* 15: 661, 1938.
3. Rauh, Louise W.: Incidence of Heart Disease in School Children, *AM. HEART J.* 18: 705, 1939.
4. Paul, J. R., Harrison, E. R., Salinger, R., and DeForest, G. K.: Social Incidence of Rheumatic Heart Disease. A Statistical Study in New Haven School Children, *Am. J. M. Sc.* 188: 301, 1934.
5. Sutton, L. P.: Observations on Certain Etiologic Factors in Rheumatism, *AM. HEART J.* 4: 145, 1928.
6. Ash, R.: Prognosis of Rheumatic Infection in Childhood; Statistical Study, *Am. J. Dis. Child.* 52: 280, 1936.

OBSERVATIONS ON THE PRODUCTION OF MYOCARDIAL DISEASE WITH ACETYLCHOLINE

RICHARD G. HORSWELL, M.D.

BOSTON, MASS.

HALL, et al.,^{1, 2} have reported that they were able to produce severe myocardial and coronary artery damage, resulting in myocardial failure, in six out of eight dogs, using injections of a 1:10,000 solution of acetylcholine, administered intravenously over a period of one and one-half hours daily. Their animals developed cardiac symptoms and died of heart failure after 19 to 227 consecutive daily injections. Cardiac murmurs first appeared in their older dogs after 12 to 19 injections, and in the younger ones murmurs were noted after 34 to 136 injections. In the hearts at autopsy they found areas of hyalinization, with developing fibrosis, hyaline degeneration of the media of medium and smaller sized arteries, with fibrosis, recent infarcts of the myocardium, thrombosis of many branches of the coronary arteries, recanalization of occluding thrombi, fatty degeneration of the myocardium about infarcted areas, and large areas of fibrosis. These changes were noted only in the old dogs. In the young animals they found no arterial changes, but reported mild to severe hyaline degeneration of the myocardium, a few scattered hemorrhagic areas with cellular infiltration, and very recent infarcts of the papillary muscle. The authors attributed the effect to a prolonged parasympathetic overbalance of the autonomic nervous system, and to confirm this hypothesis they reported similar lesions in dogs that had been adrenalectomized³ and in other animals after continuous electrical stimulation of the vagi.⁴

In undertaking an experimental study of "chronic myocarditis," an attempt has been made to produce myocardial and coronary artery damage, following, with certain modifications, the method described by Hall, et al.

METHOD

Four male and four female dogs of mixed breeds, ranging in weight from 8 to 22 kg., were selected. D5 was young, D6 very old, and the remaining six animals were middle-aged. Injections, under sterile precautions, were begun after a preliminary period of observation and training. The technique described by Hall was used, both for preparing the concentrated acetylcholine solution (each c.c. contained 25 mg.), and for the daily injections, with the exception that the concentrated acetylcholine hydrobromide (Eastman) was given in 250 c.c. of normal saline instead of 500 c.c., and the unanesthetized animals were injected only six days a week. The prescribed dose of 50 mg. of acetylcholine per dog, regardless of size, was given each day, at the outset. Such a dose produced no noticeable cardiac response after the initial tachycardia had subsided. Consequently, the

From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass.

Received for publication Sept. 28, 1940.

amount was soon increased sufficiently to attain a maximum cardiac effect throughout the ninety-minute period. (A tachycardia of over two hundred beats per minute was maintained if at all possible.) No standard dose was given because of the wide variation in the tolerance of the individual animals. The use of a buffered concentrated solution of acetylcholine was also discontinued because the compound was relatively unstable when in solution; thereafter, the crystalline material, in accurately weighed amounts, was added directly to the saline solution just before starting the infusion.

The heart rate and rectal temperature were recorded before starting each injection, and during the infusion the heart rate was checked at ten-minute intervals. Electrocardiograms, the femoral artery blood pressure, and blood cell counts were taken from time to time during the series of injections. Each animal was weighed at weekly intervals.

After two animals had been given sixty injections, two ninety injections, and four 100 injections, a blood culture, electrocardiogram, roentgenogram of the heart, and complete blood cell count were obtained on all of the animals. Measures were then taken to produce acute dilatation of the heart, first, by massive intravenous infusions of normal saline at a rapid rate, and, second, by vigorous, exhausting exercise.

Following a subsequent rest period of four months, an electrocardiogram and roentgenogram of the heart were again taken on each dog. One of the animals that had received 100 injections, D3, was sacrificed. Of the remaining animals, two, D4 and D7, were allowed to become pregnant; the rest were given a second course of injections. In this series three dogs survived 127 injections and were then sacrificed.

At autopsy, all arteries of the thorax and abdomen which were large enough to admit the tip of a pair of fine scissors were opened and examined. The coronary vessels were opened and inspected before the fresh heart was cleaned and weighed. Sections were taken routinely from both auricles, the interauricular septum, the right and left ventricular walls, the apex, the papillary muscles, the valves, and the interventricular septum, as well as from the lung, liver, kidney, pancreas, spleen, intestine, adrenal gland, and skeletal muscle. Similar sections from a number of normal hearts were studied for comparison.

TABLE I

DOG	WEIGHT	SEX	FIRST SERIES OF INJECTIONS			SECOND SERIES OF INJECTIONS		
			NO.	DAILY DOSE INCREASED FROM	AVERAGE DAILY DOSE	NO.	DAILY DOSE INCREASED FROM	AVERAGE DAILY DOSE
	<i>kg.</i>			<i>mg.*</i>	<i>mg.</i>		<i>mg.</i>	<i>mg.</i>
1	24	M	100	50 to 800	260	56	300 to 500	420
2	14	F	101	50 to 500	240	89	100 to 250	150
3	24	M	100	50 to 1000	360	--	--	--
4	17	F	90	50 to 1100	445	4	500 to 600	535
5	23	M	100	100 to 1000	420	127	250 to 500	415
6	22	M	91	75 to 800	320	125	250 to 500	385
7	17	F	60	100 to 600	280	--	--	--
8	8	F	60	100 to 800	325	126	200 to 500	370

*Mg. of acetylcholine necessary to maintain a heart rate of 200 beats per minute throughout the 90-minute injection period.

RESULTS

The essential data are presented in Tables I and II. It is to be noted that cardiac murmurs were produced in only two of the eight dogs. In D4 it appeared after twelve injections, and, in D7, after forty-six injections. Both dogs were pregnant at the time. The systolic mur-

TABLE II

DOG	TOTAL NO. OF INJECTIONS	CARDIAC MURMURS APPEARED	SIGNS OF HEART FAILURE	AURICULAR FIBRILLATION PRODUCED	P-R INTERVAL (SEC.)	OTHER EKG CHANGES	CAUSE OF DEATH	HISTOLOGIC EVIDENCE OF SCLEROSIS	MYOCARDIAL INFARCTIONS	HV/BW RATIO*
1	156	No	No	Frequently	0.12	None	Ventricular Fibrillation	None	None	0.0074
2	190	No	No	Frequently	0.08	None	Ventricular Fibrillation	None	None	0.0066
3	100	No	No	Rarely	0.12	None	Sacrificed	None	None	0.0060
4	94	After 12 Injections	Yes	Never	0.12	M-shaped QRS ₂ Elevated ST ₂₋₃	Pneumonia and Cardiac Failure†	None	None	0.0075
5	227	No	No	Rarely	0.12	None	Sacrificed	None	None	0.0069
6	216	No	No	Occasionally	0.10	Depressed ST ₂₋₃	Sacrificed	None	Small area in papillary muscle, old	0.0053
7	60	After 46 Injections	No	Frequently	0.12	None	Pneumonia	None	None	0.0057
8	186	No	No	Rarely	0.10	None	Sacrificed	None	Old area in papillary muscle of L. V.	0.0088

* Fresh total heart weight / Body weight = 0.00798, with a minimum of 0.00690 and a maximum of 0.00994.³

† Primarily failure of the right ventricle, caused by tricuspid insufficiency.

mur in D4 persisted and increased in intensity, whereas the murmur of D7 disappeared during the four-month rest period. None of the animals died of cardiac failure. Two dogs (D1, after 156 injections, and D2, after 189 injections) died suddenly while being infused, presumably as a result of ventricular fibrillation, for both of them had auricular fibrillation just prior to death. These two animals had auricular fibrillation during almost every injection, whereas only rarely did any of the others, with the exception of D7, develop fibrillation. Pneumonia was the cause of two deaths. The remaining four were sacrificed. Throughout the study, all the dogs seemed to be in good health; they gained weight and enjoyed normal activity. The acute effects which were noted during the daily acetylcholine infusions were identical with those described by Hall, i.e., tachycardia, lacrimation, salivation, vomiting (no hematemesis, however), and diarrhea, usually with melena; and, when the amount of acetylcholine per minute was increased to the maximum tolerance of the animal, extrasystoles, dropped beats, auricular fibrillation and flutter, as well as marked dyspnea (even apnea), were observed. There was no roentgenologically demonstrable increase in the size of the heart except in the case of D4, in which a 12 per cent enlargement was found. The electrocardiograms remained essentially unchanged throughout the entire period. In no instance did the P-R interval measure more than 0.14 second. At the conclusion of the first series of injections, *Staphylococcus albus* was grown from the blood of D4. No cultures were taken on the surviving dogs at the conclusion of the second series of injections.

MORPHOLOGIC CHANGES

Heart.—The hearts of six of the animals were grossly normal. The $\frac{HW}{BW}$ ratios, based on figures published by Harmann,⁵ were within normal limits (see Table II). The right side of the heart of D4 was dilated, and an area in the anterior aspect of the right ventricular wall was markedly thinned. The tricuspid valve was fenestrated and incompetent, and was very edematous when examined histologically. Microscopically, the thinned area in the anterior aspect of the right ventricle showed only replacement of the myocardium by fat cells, with no fibrosis or cellular reaction and no occluded vessels.

In a papillary muscle of the left ventricle of D6 a small area of fibrosis was found, and on the mitral valve a fresh verrucous lesion, containing colonies of staphylococci, was noted. In D8 there was a small calcified lesion in a papillary muscle of the left ventricle. No recent infarctions or occlusions of the coronary arteries could be found in any of the hearts (see Table II). On microscopic examination, rarely a small artery showed slight thickening of the media, but not more than was found in the control hearts.

Lungs.—Passive congestion was noted in D2 and D4.

Liver.—The liver of D4 was contracted, hard, and nodular, resembling cardiac cirrhosis. That of D2 showed acute passive congestion, and that of D6, chronic passive congestion.

Pancreas.—Agonal dilatation of the arterioles, with fresh petechiae, was found throughout the pancreas of D1 and D2.

Spleen.—A few of the spleens contained abnormal amounts of pigment deposits.

Kidneys.—Except for both kidneys of D6, which were the seat of extensive acute and chronic suppurative nephritis, only an occasional area of infarction was found.

Intestinal Tract.—The mucosa of the stomach was essentially negative. In all the dogs there were shallow depressions, measuring from 1 to 3 cm. in diameter, which extended from the pylorus to the appendix, were covered with epithelium, and varied in number from six to twenty per animal. On histologic examination, none of them had the characteristics of a peptic ulcer; they were composed of markedly thinned mucosa overlying collections of lymphoid cells. The mucosa of the intestine of the two dogs which had died during an injection was beefy red from an inch beyond the pylorus to the rectum; that of the other dogs was a purplish pink.

Adrenal Gland.—Nothing abnormal was observed.

Arterial Tree.—No atheromata or occlusions were found in the aorta or its branches as far as they could be traced.

DISCUSSION

An attempt to produce myocardial degeneration with injections of acetylcholine was unsuccessful, even though each dog was given the maximum dose it could tolerate. In addition, to avoid the possibility of any decomposition of the acetylcholine before it reached the blood stream of the animal, the crystals were added directly to the normal saline just before each injection. Cardiac murmurs were heard in only two of the animals. Cardiac disability developed in one dog, and was evidently caused by tricuspid insufficiency resulting from healed endocarditis. Two acute deaths took place, probably because of ventricular fibrillation; post-mortem examination of these hearts was entirely negative. The electrocardiograms, for the most part, remained normal, and the P-R interval was not prolonged in any instance. (Hall noted that the P-R interval increased to 0.4 second in one case.) There was no histologic evidence of vascular changes and myocardial lesions, for sections from control animals showed comparable changes.

Inasmuch as Hall, et al., have stated that, with a daily dose of 50 mg. of acetylcholine, they noted the appearance of cardiac murmurs after 9 to 136 consecutive injections, and death as a result of cardiac failure after 21 to 227 injections in six out of eight dogs, it was felt that their method had been given a fair trial. The fact that, in the study

here reported, a rest period of four months was given to the animals does not render the results invalid because the production of myocardial disease should be an accumulative process.

Gilbert and LeRoy,⁶ in substantiation, have closely adhered to the method employed by Hall, et al., using first a dose of 50 mg., but later increasing it to 100 mg., of acetylcholine daily, and have given daily injections totaling 606, 558, 546, 531, 510, 458, and 430 mg., respectively, to seven dogs without producing more than a minor degree of myocardial and coronary artery damage. None of their animals developed signs of cardiac failure or significant electrocardiographic changes, although they noted the appearance of systolic murmurs in some of them.

CONCLUSIONS

Intravenous injections of acetylcholine hydrobromide were given over a ninety-minute period, six days a week, for a total of 101, 100, 100, 100, 91, 90, 60, and 60 mg., respectively, to eight dogs. Following a subsequent rest period of four months, six of the dogs received additional injections numbering 4, 56, 89, 125, 126, and 127, for a final total of 227, 216, 190, 186, 156, 100, 94, and 60 injections, respectively. The daily dose, which averaged from 150 to 445 mg., was increased from 50 mg. to as high as 1,100 mg., depending on the degree of tolerance to the drug manifested by the individual animal. Two of the dogs developed cardiac murmurs, one after twelve injections, the other after forty-six injections; both were pregnant at the time, and one of them had a bacterial endocarditis involving the tricuspid valve. Two dogs died while being injected, probably from ventricular fibrillation. The electrocardiograms and morphologic changes in all the hearts were comparable to those of the control dogs.

An attempt to produce severe coronary artery damage and myocardial failure in dogs by intravenous acetylcholine injections was unsuccessful.

I wish to thank Dr. Nathan Rudo for interpreting the pathologic data.

REFERENCES

1. Hall, G. E., Ettinger, G. H., and Banting, F. G.: An Experimental Production of Coronary Thrombosis and Myocardial Failure, *Canad. M. A. J.* 34: 1, 1936.
2. Hall, G. E.: Experimental Heart Disease, *Ann. Int. Med.* 12: 907, 1939.
3. Hall, G. E., and Cleghorn, R. A.: Cardiac Lesions in Adrenal Insufficiency, *Canad. M. A. J.* 39: 126, 1938.
4. Manning, G. W., Hall, G. E., and Banting, F. G.: Vagus Stimulation and the Production of Myocardial Damage, *Canad. M. A. J.* 37: 314, 1937.
5. Herrmann, G. R.: Methods of Dividing Hearts: With Sectional and Proportional Weights and Ratios for Two Hundred Normal Dogs' Hearts, *AM. HEART J.* 1: 213, 1925.
6. Gilbert, N. C., and LeRoy, G. L.: Personal Communication.

DEPROTEINATED PANCREATIC EXTRACT (DEPROPANEX)

II. EFFECT OF INTRAVENOUS ADMINISTRATION IN RABBITS*

M. STEPHEN SCHWARTZ, M.D., MARTIN M. FISHER, M.D.,
IRVING S. WRIGHT, M.D., AND A. WILBUR DURYEE, M.D.
NEW YORK, N. Y.

IN UTILIZING any therapeutic agent, the most efficacious method of administration is naturally desired. In the use of pancreatic extracts, intravenous administration has been associated with unfavorable reactions in the past. N. W. Barker and R. W. Graham¹ stated that when pancreatic extracts were injected intravenously into animals, toxic effects were noted. J. B. Wolfe,² similarly, has warned against the intravenous administration of these extracts. However, with the development of deproteinated pancreatic extract, which is practically protein-free, as well as free of insulin, histamine, and acetylcholine, the possibility of intravenous administration was considered more favorably. The present study was instituted in order to note the effects of large amounts of deproteinated pancreatic extract when administered intravenously to rabbits.

METHODS AND MATERIALS

Twelve rabbits which weighed from four to eight pounds, were approximately five months old, and were all males except one, were used. Three of this group were anesthetized by intraperitoneal injections of sodium amytal (60 milligrams per kilogram of body weight). The nine others were unanesthetized. The rabbits were bound down to a rabbit board, and deproteinated pancreatic extract was administered by intravenous infusion to seven rabbits and by a multiple syringe method to five. The routine intravenous infusion drip apparatus was used for the slow method, and a multiple syringe for the rapid method. The time of administration was noted, and the onset of the rabbits' reactions were charted in the order of their occurrence. Two animals, used as controls, received saline by the intravenous infusion method. Electrocardiograms were taken before and after the administration of deproteinated pancreatic extract in several rabbits. Six rabbits were given deproteinated pancreatic extract by intravenous infusion at a rate of 1.1 to 1.5 c.c. per minute (Group I, see Table I). One rabbit was given deproteinated pancreatic extract by the multiple syringe method at a rate of 1.7 c.c. per minute, and four received the extract by the same method at a rate of 3 to 8 c.c. per minute (Group II).

RESULTS

No signs were noted after the administration of the first 5 to 10 c.c. of deproteinated pancreatic extract intravenously. Salivation usually occurred after the animal had received 15 c.c. The subsequent signs.

From the Vascular Clinic, Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University.

*Aided by a grant from Sharpe and Dohme, Inc.

Received for publication Oct. 5, 1940.

TABLE I
TOXICITY OF DEPROTEINATED PANCREATIC EXTRACT INJECTED INTRAVENOUSLY
IN RABBITS

RABBIT NO.	SEX	WEIGHT KG.	DEPROTEINATED PANCREATIC EXTRACT				METHOD
			TOTAL AMOUNT C.C.	C.C. PER KG. BODY WEIGHT	TOTAL INJECTION TIME MIN.	RATE C.C. PER MIN.	
<i>Group I</i>							
1003	M	2.2	290	131.8	255	1.1	Infusion
1006	M	2.7	260	96.3	205	1.2	Infusion*
1002	M	2.0	153	76.5	102	1.5	Infusion
							Anesthetized
1001	M	2.0	100	50.0	101	1.0	Infusion*
1005	M	1.8	87	48.3	60	1.4	Infusion
43	M	2.0	73	36.5	60	1.2	Infusion
2	M	2.4	100	41.7	60	1.7	Syringe
							Anesthetized
<i>Group II</i>							
46	M	2.0	38	19.0	13	3.0	Syringe
568	M	3.6	48	13.3	15	3.2	Syringe
							Anesthetized
6	F	3.2	55	17.2	7	8.0	Syringe
4	M	3.0	54	18.0	6	9.0	Syringe
							Anesthetized
<i>Controls</i>							
1007	M	2.4	250 c.c. saline	104.2	60	4.0	Infusion*
1006	M	2.7	200 c.c. saline	74.1	70	2.8	Infusion*

*Animal survived.

mostly parasympathomimetic, occurred at variable intervals of administration. Among the prominent manifestations, in the order of their occurrence, were lacrimation, rhinorrhea, increased muscle tone to tremors, increased peristalsis to diarrhea, involuntary micturition, rapid respiration, rapid pulse to irregular pulse, generalized convulsions, and, terminally, pulmonary edema.

There was no difference in the onset of signs in those animals which were anesthetized as compared to those which were unanesthetized.

At the rate of 1.1 to 1.5 c.c. per minute (Group I), from 73 c.c. to 290 c.c. of deproteinated pancreatic extract were given by the intravenous infusion method. From 36.5 to 131.8 c.c. per kilogram of body weight were received by this group.

The one rabbit which received the extract at the rate of 1.7 c.c. per minute by the multiple syringe method tolerated 100 c.c. in sixty minutes, or 41.7 c.c. per kilogram of body weight. When the rate of administration was increased from 3 to 8 c.c. per minute (Group II), doses from 38 to 55 c.c. were sufficient to cause death; an average of 16.8 c.c. per kilogram of body weight was given to this group.

The two saline controls survived the infusions. One received 250 c.c. at a rate of 4 c.c. per minute, and the other 200 c.c. at a rate

of 2.8 c.c. per minute. The only signs noted were evanescent tremors. One of these rabbits, No. 1006, was subsequently submitted to an infusion of deproteinated pancreatic extract and tolerated 260 c.c. of the extract without succumbing.

Rabbit No. 1001 survived 100 c.c. of deproteinated pancreatic extract, when the experiment was terminated. Thus these figures could have been higher had the rabbits been allowed to receive more deproteinated pancreatic extract. No delayed reaction or latent effects were noted in these animals which survived. Electrocardiograms revealed no significant changes, but, because the series was small, no definite evaluations can be made.

DISCUSSION

From this study, it seems apparent that further investigations in the direction of intravenous administration might be worth while. No untoward reactions in man were noted in giving over 1,000 injections of this substance intramuscularly in the hip, in doses of 3 c.c. three times a week. We have previously reported its use, intravenously, in twenty patients without severe systemic reactions. Because protein is practically absent from this preparation, danger from this component of earlier extracts is eliminated. Since rabbits weigh only one thirty-fifth as much as adult human beings, and can tolerate massive doses per kilogram of body weight, further investigative work, using slow intravenous administration of small doses of deproteinated pancreatic extract in man, can be instituted without great risk. It is only by studying a large group of patients, over a long period of time, that conclusions can be drawn as to the relative value of this substance in the treatment of peripheral vascular disease.

CONCLUSIONS

1. Deproteinated pancreatic extract is a relatively nontoxic substance when injected intravenously into rabbits.

2. The slower the administration of the extract, the greater the tolerance of the animal to still larger doses.

REFERENCES

1. Barker, N. W., and Graham, R. W.: The Treatment of Hypertension, *Med. Clinics N. America*, Mayo Clinic Number, 1021-1031 (July), 1939.
2. Wolffe, J. B.: Personal Communication.
3. Fisher, M. M., Duryee, A. W., and Wright, I. S.: Deproteinated Pancreatic Extract (Depropanex): Effect in the Treatment of Intermittent Claudication Due to Arteriosclerosis Obliterans, *AM. HEART J.* 18: 425, 1939.

A COMPARISON OF LEADS IV R AND IV F

IRVING M. LIEBOW, M.D., AND EDWARD H. CUSHING, M.D.
CLEVELAND, OHIO

CHEST leads were first used clinically by Wolferth and Wood,¹ in 1932. Within a few years precordial leads came into widespread use. Following this there developed confusion because of lack of uniformity in nomenclature and technique. In 1938 a report of the Committee for the Standardization of Precordial Leads appeared,² and a few months later the Committee published further recommendations in a supplementary report.³ Of all the chest leads considered, Leads IV R* and IV F† were advised for ordinary purposes. Furthermore, the Committee expressed preference for Lead IV F, but suggested that more investigation of the apical leads would be necessary before final judgment.

Following the suggestions of the Committee, many workers investigated the relative values of the two apical leads. Edwards and Vander Veer,⁴ using the six standard positions in CR, CL, and CF, in addition to Leads IV R and IV F, concluded that Lead IV R was the one of choice provided the heart is not appreciably enlarged. (In the latter event the precordial electrode is never to be placed farther to the left than the anterior axillary line.) Likewise, Wood and Selzer,⁵ in a study of Leads IV R and IV F and several other chest leads, came to the conclusion that the right arm site for the indifferent electrode was most informative, and advised its routine use in preference to the left leg. Geiger⁶ is of the opposite opinion. He found significant discrepancies between Leads IV R and IV F in sixty-four out of 400 records. In fifty-five of these records the diagnostic abnormalities were more marked in IV F, and in only nine were they more marked in IV R. He concluded that Lead IV F was distinctly better than Lead IV R.

Shortly after the publication of the Committee's recommendations,^{2, 3} we began to take both apical leads routinely, in addition to the standard limb leads. In view of the diversity of opinions we have compared Leads IV R and IV F in our cases.

METHOD

Eight hundred seven electrocardiograms were made on 389 patients. These included the standard limb leads and Leads IV R and IV F. The number of records on each patient ranged from one to fourteen. The patients were all adults who had been sent to the laboratory because they were known to have, or were suspected of having, heart disease. Beyond this no selection of patients or electrocardiograms was made.

From the Department of Medicine, Western Reserve University, and the Lakeside Hospital, Cleveland.

Received for publication Oct. 9, 1940.

*Indifferent electrode on the right arm; exploring electrode over the apex.

†Indifferent electrode on the left leg; exploring electrode over the apex.

The position of the subjects varied from recumbent to sitting at slightly less than 90 degrees. All records were taken on a Cambridge "Hindle" electrocardiograph. The patient's resistance was in all instances 2,000 ohms or less. The galvanometer connections were made in such a way that relative positivity of the precordial electrode was represented by an upward deflection.² The interpretation of each electrocardiogram was made upon consideration of all the leads taken.

ANALYSIS

The purpose of our study was to ascertain whether one of the apical leads was *significantly* more diagnostic than the other. To accomplish this we have classified Leads IV R and IV F in relation to each other as "similar" and "dissimilar." If both were normal or both were abnormal they were considered similar; on the other hand, if one was normal and the other was abnormal they were considered dissimilar. An apical lead was termed abnormal if (a) the initial positive deflection was absent, or 2 mm. or less in height;^{7, 8} (b) the S-T junction was elevated more than 2 mm. or depressed more than 1 mm.;⁹ (c) the T wave was other than upright^{9, 10} or was upright and less than 1 mm. in amplitude.^{9, 11, 12*}

The similar records comprised a large number (767) of IV R and IV F leads, so that a brief description of the general characteristics of their complexes may be a valuable addition to the already available information concerning them. Forty dissimilar records were found among the 807 records compared in the above manner, and these will be analyzed separately.

ELECTROCARDIOGRAMS IN WHICH LEADS IV R AND IV F WERE SIMILAR

P Waves.—The P waves in 715 records were compared; several records were omitted because of the presence of auricular fibrillation. In Lead IV R the P wave was a positive deflection in 694 (97 per cent), and a negative deflection in 5 (0.69 per cent). It was isoelectric in five (0.69 per cent), and of more than one phase in eleven (1.52 per cent). Of the positive deflections, only thirty-two were less than 1 mm. in amplitude. Thus slightly more than 95 per cent of the positive P waves were 1 mm. or more in size, and 92.5 per cent of all P waves in IV R were both positive and at least 1 mm. in amplitude. The maximum amplitude was 4 mm.

In Lead IV F the P wave was positive in 266 (37.2 per cent), isoelectric in 209 (29.2 per cent), and negative in 191 (26.7 per cent). It was of more than one phase in forty-nine (6.84 per cent). Of the positive deflections, only seventy-three (27.4 per cent) were 1 mm. or more in height. Thus only 10.2 per cent of all P waves in this lead were both positive and at least 1 mm. in amplitude. The maximum amplitude was 2 mm.

*The references cited above give varying figures for the minimum amplitude of T in Leads IV R and IV F. A minimum of 1 mm. was chosen arbitrarily, after consideration of these figures, as most representative.

In the 715 cases, P in IV F was similar to P in IV R in ten (1.39 per cent), and P in IV R was exceeded in size by P in IV F in ten (1.39 per cent). The P wave in Lead IV R was therefore more often positive and more often larger than P in Lead IV F. Furthermore, P in IV R was usually positive and easily measured, whereas P in IV F was isoelectric, or so small a positive or negative deflection that its identification was difficult.

QRS Complexes.—A few records were omitted because large R or S waves extended beyond the edge of the record. Seven hundred twelve complexes were analyzed. Of these, the algebraic summation of the complexes in both IV R and IV F were in the same direction in 615 (86.4 per cent), and in different directions in ninety-seven (13.6 per cent). In this latter group of ninety-seven tracings, QRS in IV R was positive in eighty, and QRS in IV F was positive in the remaining seventeen.

The amplitude of QRS was calculated in the 615 cases in which the direction was the same. The complexes were considered to be of equal amplitude if the algebraic summations were within 2 mm. of each other. With this classification, QRS of IV R and IV F were equal in 165 (26.8 per cent). The QRS of IV R was larger than that of IV F (2.5-27 mm.; average 7.46 mm.) in 340 (55.3 per cent) and the QRS of IV F was larger than that of IV R (2.5-22 mm.; average 5.41 mm.) in 110 (17.9 per cent). In all 712 cases, i.e., including those considered equal, QRS in IV R was larger than QRS in IV F (average 4.09 mm.).

S-T Junction.—In considering the S-T junctions of the electrocardiograms with similar apical leads, all records in which a digitalis effect was noted were omitted. Seven hundred seven records were studied. The junction was isoelectric in both leads in 338 records (47.8 per cent), and deviated equally (less than 1 mm. difference) in 265 (37.5 per cent). In fifty-two records (7.4 per cent) the deviation was more positive (2 mm. or more difference) in IV R, and the same held true in an equal number of cases for IV F.

In the last two groups (104 records) the deviation of the S-T junction was positive in both IV R and IV F in thirty-seven cases, in twenty-four of which IV R was more positive than IV F. In these groups the deviation was negative in both IV R and IV F in twenty-five cases, in sixteen of which IV R was more negative than IV F.

Thus it is seen that the S-T junction in Leads IV R and IV F was isoelectric in about half the cases, and deviated equally in about four-fifths of the remaining cases. When the junction deviated unequally (1 mm. or more difference) but in the same direction, the deviation, whether positive or negative, was more marked in IV R.

T Waves.—The T waves of the 754 records were analyzed. In 483 (63.9 per cent of the total), T was positive in both leads. Among these 483 in which T was positive in both, T in IV R was larger than T in IV F in 357 (73.9 per cent), and smaller in fifty-four (11.2 per cent). They

were equal in seventy-two (14.9 per cent). In 199 records, T was negative in both leads; it was of the same amplitude in thirty-seven (18.6 per cent), of greater negative amplitude in IV F in ninety-one (45.7 per cent), and of greater negative amplitude in IV R in seventy-one (35.7 per cent). There remained seventy-two records in which the T waves were neither both positive nor both negative. Among these seventy-two were twenty-one records of anterior and apical infarction in which Leads IV R and IV F were considered similar because both were diagnostic, but in which the T waves varied. In nineteen of these twenty-one records T in IV F was negative, whereas T in IV R was diphasic or of abnormally small positive voltage. The reverse held true in the remaining two records. In this same group of seventy-two there were ten records of posterior and basal infarction, among which T in IV F was more abnormal than T in IV R seven times, with the reverse holding true in the remaining three.

ELECTROCARDIOGRAMS IN WHICH LEADS IV R AND IV F WERE DISSIMILAR

In forty of the 807 records which were studied, Leads IV R and IV F differed significantly from each other. These differences were noted in cases of myocardial infarction, in records showing a digitalis effect, and in a miscellaneous group. The dissimilarities will be discussed under these headings.

MYOCARDIAL INFARCTION

Anterior Infarction.—In cases of anterior myocardial infarction, 209 records on sixty-five patients were available. Leads IV R and IV F differed in 3.8 per cent (eight records). In seven out of eight records Lead IV F was more diagnostic; the difference was confined to an inverted, diphasic, or small T wave in IV F, with a normal T in IV R. The abnormal T in IV F appeared earlier and lasted longer.

Posterior Infarction.—In cases of posterior myocardial infarction, 161 electrocardiograms on fifty-one patients were analyzed. Leads IV R and IV F differed in 6 per cent (ten) of the records. Diagnostic abnormalities were found in Lead IV R in six cases and in Lead IV F in four cases. The abnormalities were confined to (a) diphasic T waves; (b) abnormal depression of the S-T junction; (c) a combination of (a) and (b); and (d) inversion of the T wave. The diphasic T wave occurred in six of the ten records.

Miscellaneous Group.—This group includes thirty-one records on eight patients. Three patients were thought to have both anterior and posterior myocardial infarction, and three were thought to have infarction of the lateral wall of the left ventricle (proved in one case by post-mortem examination). The seventh and eighth patients were thought to have myocardial infarction, but the infarcted area could not be localized, and the diagnosis itself was not definitely established. Four dis-

similar records in two cases were noted; the abnormalities occurred in Lead IV F. In two of five records from a patient with combined anterior and posterior myocardial infarction, Lead IV R was normal but Lead IV F showed abnormal depression of the S-T junction. In two of five records from a patient with questionable infarction the standard leads and Lead IV R were normal, but T in IV F was of abnormally low amplitude.

DIGITALIS EFFECT

A digitalis effect was noted in fifty-three records on thirty-nine patients. In forty-eight of the fifty-three, changes of the S-T junction or the T wave were sufficiently alike in both leads to be considered similar, but the changes were slightly more marked in Lead IV R in all forty-eight records. In the remaining five records (9.4 per cent) Lead IV F was normal, and Lead IV R alone indicated the effect of digitalis.

MISCELLANEOUS GROUP

Lead IV F Abnormal.—Of fourteen records on six patients with various types of disease, nine showed an abnormal Lead IV F but a normal IV R. The abnormalities were confined to the T wave, which was either diphasic (six instances), inverted (two instances), or isoelectric (one instance). The abnormal T wave appeared earlier in IV F than in IV R in a patient with bronchopneumonia, and lasted longer in a patient with pulmonary embolism. Abnormal changes were noted in three cases of angina pectoris, but the records were not exactly comparable because one patient had hypertension, another had normal blood pressure, and the third had had a Beck cardiac anastomosis two years before.

Lead IV R Abnormal.—Of twelve records on four patients with various types of disease, four showed an abnormal Lead IV R but a normal IV F. In one of several records taken on two patients with hypertension, Lead IV F was normal, whereas in Lead IV R the S-T junction was depressed and the T wave inverted in one case, and the T wave diphasic in the other. In a case of hemopericardium the expected elevation of the S-T junction was diagnostically more marked in Lead IV R. In a patient, aged 29 years, with a history of streptococcus infection of the throat seven years previously and subsequent paroxysmal tachycardia, Lead IV F was normal but T in IV R was markedly inverted.

COMMENT

Leads IV R and IV F differed significantly from each other in only a small percentage (5 per cent) of cases. These differences were not found consistently in any one lead in any given group of electrocardiograms, save in those showing a digitalis effect, in which records Lead IV R was distinctly superior. In the other groups the abnormalities were unevenly divided.

Lead IV F had a numerical superiority of twenty-four to sixteen in relation to the dissimilar electrocardiograms, but a superiority of only seventeen to fourteen in relation to the number of patients these records represented. There was agreement between Lead IV R and IV F in 95 per cent of the 807 records. Significant variations from normal were observed in Lead IV F and not in Lead IV R in an additional 3 per cent (twenty-four records), whereas in 2 per cent (sixteen records) the significant variations from normal were observed only in Lead IV R.

SUMMARY OF ALL RECORDS

1. Eight hundred seven electrocardiograms, with the standard leads and Lead IV R and IV F, were analyzed with a view to comparing the two apical leads.

2. Using the criteria described above, Leads IV R and IV F were found to be dissimilar (significantly different) in forty records (4.9 per cent).

3. In the 767 records in which Leads IV R and IV F were similar, the P wave, the QRS complex, and the T wave were larger and more positive, on the whole, in Lead IV R than in Lead IV F.

4. In anterior myocardial infarction with dissimilar apical leads (3.8 per cent), Lead IV F was diagnostic earlier and longer (seven out of eight records).

5. In posterior myocardial infarction with dissimilar apical leads (6 per cent), Lead IV R was the abnormal lead in six out of ten records.

6. In one doubtful and one unusual type of myocardial infarction, Lead IV F was abnormal in all of four dissimilar records.

7. A digitalis effect was always more marked in Lead IV R, and in five cases was the only one of the two apical leads to display it.

8. In a miscellaneous group comprising thirteen dissimilar records, Lead IV F was the abnormal lead in nine records, and Lead IV R in four records.

9. In the great majority of all the dissimilar records the changes were confined to abnormalities of the T wave.

10. Of the forty dissimilar electrocardiograms, the abnormalities were noted in Lead IV F in twenty-four (3 per cent of total) and in Lead IV R in sixteen (2 per cent of total). In relation to the number of patients with dissimilar records, Lead IV F was abnormal in only seventeen cases, and Lead IV R in fourteen cases.

CONCLUSIONS

1. The use of both Leads IV R and IV F results in slightly greater accuracy than the use of either lead alone.

2. If only one apical lead is to be employed, either Lead IV R or Lead IV F may be used to the exclusion of the other without appreciable prejudice to the best electrocardiographic diagnosis.

REFERENCES

1. Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am. J. M. Sc.* 183: 30, 1932.
2. Standardization of Precordial Leads. Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland, *AM. HEART J.* 15: 107, 1938.
3. Idem: *AM. HEART J.* 15: 235, 1938.
4. Edwards, Joseph C., and Vander Veer, Joseph B.: A Study of the Chest Leads of the Electrocardiogram with an Evaluation of the Positions of the Precordial Electrode, *AM. HEART J.* 16: 431, 1938.
5. Wood, P., and Selzer, A.: Chest Leads in Clinical Electrocardiography, *Brit. Heart J.* 1: 49, 1939.
6. Geiger, Arthur J.: A Comparative Study of Precordial Leads IV R and IV F, *AM. HEART J.* 18: 715, 1939.
7. Vander Veer, Joseph B., and Edwards, Joseph C.: The Significance of Small and Absent Initial Positive Deflections in the Chest Lead, *Am. J. M. Sc.* 197: 663, 1939.
8. Contratto, A. W., Robinson, R. W., and Levine, S. A.: The Precordial Lead, *Arch. Int. Med.* 63: 732, 1939.
9. Sorsky, Eliot, and Wood, Paul: The Use of Chest Leads in Clinical Electrocardiography, *AM. HEART J.* 13: 183, 1937.
10. Wilson, Frank N.: Recent Progress in Electrocardiography, *Proc. A. Life Insur. M. Dir.* 24: 96, 1938.
11. Barnes, Arlie R.: Electrocardiographic Patterns: Their Diagnostic and Clinical Significance, Charles C Thomas, Springfield, Ill., Publisher, 1940.
12. Kline, Edward M.: Chest Leads in 100 Normal Individuals, Unpublished Work.

Department of Reviews and Abstracts

Selected Abstracts

Corcoran, A. C., and Page, Irvine H.: Arterial Hypertension. Correlation of Clinical and Experimental Observations. J. A. M. A. 116: 690, 1941.

Angiotonin, or renin plus activator, when injected into animals produces those effects which have been shown to characterize arterial hypertension in man; namely cardiac augmentation, arteriolar constriction, and constriction of the efferent arterioles of the kidneys. This suggests the possibility that angiotonin is involved in the pathogenesis of essential and malignant hypertension in man.

The endocrine system, notably the adrenal cortex and hypophysis, appears to participate indirectly in that its secretions maintain the blood vessels and heart in a state receptive to hypertensive stimuli. The nervous system may play a similar part, especially in some types of hypertension in man in which the high state of nervous organization may even make it a prepotent factor.

The clinical picture and course of each case of hypertension is therefore probably a composite of the degree and kind of renal, endocrine, and nervous participation.

AUTHORS.

Christian, Henry A.: Earlier Diagnosis of Subacute *Streptococcus Viridans* Endocarditis. J. A. M. A. 116: 1048, 1941.

Since patients with subacute *Streptococcus viridans* endocarditis so often come to the hospital without a diagnosis or with a wrong diagnosis, it is apparent that relatively few practitioners are aware of the usual early clinical picture of this disease.

The chief early symptoms in the 150 patients I have examined resulted from toxemia. They were complaints indicative of (a) malaise and fever in 52.6 per cent of cases at onset and 71.3 per cent at onset and in the early days of the disease; (b) joint or muscle pains in 42 per cent at or near onset; and (c) nausea or loss of appetite in 16 per cent at onset and in the early days of the disease.

If these symptoms appear in a patient known or found to have evidence of chronic valvular or congenital disease of the heart and persist for more than one week without the development of evidence of other definite disease, the probability of bacterial endocarditis is great.

If in these patients embolic phenomena appear or a blood culture is positive, a definite diagnosis of bacterial endocarditis should be made.

If the condition referred to in either of the foregoing two paragraphs occurs, appropriate chemotherapy should be begun at once.

AUTHOR.

Brown, Clark E., and Richter, Ina M.: Medial Coronary Sclerosis in Infancy. Arch. Path. 31: 449, 1941.

A case of coronary calcification in infancy is reported with data on six additional cases abstracted from the literature. This type of vascular change is part of general arterial calcification, the chief site of which appears to be the internal elastica.

Coexistent intimal proliferations are noted frequently. These may result at times in occlusion. The cause of the lesion is in doubt, although some alteration in the calcium and phosphorus metabolism is suspected.

AUTHORS.

Meiks, L. T.: *The Influence of Tonsillectomy on the Progress of Rheumatic Heart Disease.* J. Indiana M. A. 33: 666, 1940.

The present study is based on 200 patients who present definite evidence of rheumatic heart disease. Of this group of 200 cases thirty-one had had tonsillectomies before the development of any manifestation of rheumatic fever. In the remaining 169 patients admitted to the hospital after development of definite rheumatic heart disease, tonsillectomies were done eventually on seventy-nine. Of these seventy-nine patients operated upon, there were twenty-eight in whom there were valid indications. In twenty-three patients tonsillectomies were done upon questionable indications. In twenty-eight patients tonsillectomies were done only because of the presence of rheumatic heart disease. The author traces statistically the course of these 79 patients. He offers the following conclusions.

The removal of tonsils and adenoids usually does not modify the course of rheumatic heart disease, and the presence of this condition is not of itself an indication for their removal.

In the presence of definite local indication for tonsillectomy and adenoidectomy in a patient with rheumatic heart disease, it is proper that the operation be done.

The operation, as a rule, should not be done in the presence of signs of activity of the rheumatic infection.

There is occasionally an immediate recrudescence of rheumatic activity after tonsillectomy and adenoidectomy.

AUTHOR.

Hedley, O. F.: *Rheumatic Heart Disease in Philadelphia Hospitals. IV. Influence of Season and Certain Meteorological Conditions.* Pub. Health Rep. 55: 1809, 1940.

A review of the literature indicates that in Great Britain rheumatic fever and chorea occur with greatest frequency in the fall and during December and least often in the spring and early summer. The experience of most American writers suggests that in this country these conditions are most common during the late summer and fall.

In agreement with this consensus this study indicates that in Philadelphia admissions involving rheumatic fever and chorea are most frequent in the spring and least frequent in the fall. The greatest number of admissions involving rheumatic fever was in April, the fewest in October. The peak of admissions involving chorea occurred in May; the smallest number in November.

Despite the fact that admissions involving rheumatic fever occurred with greatest frequency during the first six months of the year, especially the spring, and least often during the fall, considerable variations were noted from year to year. In a study of only five years' duration, the greatest number of admissions occurred twice during April, twice during May, and once during June.

Seasonal variations of chorea were not as great as of rheumatic fever. The seasonal distribution of these conditions was only roughly comparable. There was apparently no relationship between the number of patients for these diseases.

Admissions involving these conditions did not occur with greatest frequency during the coldest months or with least frequency during the warmest months. After allowing for the possibility that several weeks had elapsed between onset and admission to hospital, it is doubtful whether the onset of the greatest number of cases

of rheumatic fever and chorea coincides with the coldest time of the year. These diseases are apparently no more common during years with low mean temperatures or following severely cold winters. Prolonged cold of winter, rather than severe cold or the onset of cold weather, seems more likely to be responsible for the increased frequency of rheumatic fever and chorea during the spring. It is difficult to dissociate the role of prolonged cold from lack of sunshine.

No relationship was indicated between the amount of precipitation and the number of patients with rheumatic fever and Sydenham's chorea.

Although admission of patients with rheumatic heart disease is more common during the spring and least frequent during the fall, seasonal variations are not as great as for rheumatic fever and chorea.

Seasonal variations of deaths from rheumatic heart disease are not as great as admissions involving rheumatic fever, chorea, or rheumatic heart disease but are somewhat greater than for deaths from all heart disease and deaths from all causes.

The seasonal distribution of the admission of patients with rheumatic conditions and of deaths from rheumatic heart disease is dissimilar in many respects to the distribution of deaths from acute coronary occlusion.

In contradistinction to strictly rheumatic conditions, practically no seasonal variations were noted in admissions or deaths from subacute bacterial endocarditis regardless of its relationship to rheumatic heart disease.

AUTHOR.

Hedley, O. F.: Rheumatic Heart Disease in Philadelphia Hospitals. V. Distribution by Locality of Rheumatic Conditions in Philadelphia. Pub. Health Rep. 55: 1845, 1940.

A review of the literature indicates a considerable lack of agreement concerning the roles of proximity to watercourses and dampness due to low altitude in the causation of rheumatic fever and chorea. The consensus of most investigations suggests that these diseases are distinctly more prevalent in areas occupied by the underprivileged than the better-to-do.

Rheumatic fever, Sydenham's chorea, and nonfatal and fatal rheumatic heart disease among hospital patients in Philadelphia tended to occur with greatest frequency in the sections of the city occupied to a large extent by the poor. This relationship was not, however, invariable. Some of the city wards in which the rentals were the lowest and the density of population the greatest did not have the greatest number of hospital admissions or deaths per 100,000 population. A low rate of admissions and deaths was noted in every city ward inhabited for the most part by persons living under reasonably favorable economic circumstances. This is doubtless due in no small measure to the fact that persons in the better-to-do economic brackets do not regularly seek admission to hospitals for the treatment of medical conditions. It is difficult to escape the impression that the conditions under study occur with the greatest frequency in sections of the city occupied by poverty-stricken persons.

These diseases tended to occur with greatest frequency in the eastern half of South Philadelphia and in a section of the midcity near the Delaware River.

These studies do not suggest that proximity to a watercourse is an important factor. The distribution of low rentals corresponded more closely to the Delaware River water front than the distribution of rheumatic fever and chorea.

Relatively low rates of admissions and deaths in hospitals from these diseases were indicated in a number of city wards occupied largely by colored persons.

The distribution of Sydenham's chorea is roughly comparable to rheumatic fever, except that a somewhat more general distribution is indicated. It is even less common than rheumatic fever in city wards largely occupied by negroes.

A more general distribution was indicated in mortality from rheumatic heart disease in hospitals than of admissions for rheumatic fever, Sydenham's chorea, and rheumatic heart disease. This suggests that the more acute or fulminating forms of rheumatic infection occur with relatively greater frequency among the extremely poor. An analogy is noted between tuberculosis and rheumatic infection.

AUTHOR.

Hines, Edgar A., Jr., and Lander, Howard H.: Factors Contributing to the Development of Hypertension in Patients Suffering From Renal Disease. J. A. M. A. 116: 1050, 1941.

The results of this study show that in a series of 264 patients who had various types of urologic diseases, those patients who had a high normal blood pressure on their visit were four to five times as likely to have hypertension subsequently as were those who had a low normal blood pressure, regardless of the type or extent of the urologic or renal lesion and regardless of whether the onset of symptoms of the disease of the urinary tract occurred before or after the original blood pressure reading. In respect to the correlation between the original blood pressure and the subsequent development of hypertension, there was little difference between the series of patients suffering from urologic disease and a control series of persons who had no renal or urologic disease. Furthermore, as far as could be determined on the basis of a study of the family histories of our patients, heredity plays a similar role in the development of hypertension associated with renal disease and, in many instances, of essential hypertension. We do not interpret our data as constituting a denial that renal disease may have been a contributing factor to the development of hypertension in some of our patients. However, these data do seem to cast some doubt on the importance of renal disease in producing hypertension in the series as a whole and call attention to the importance of exercising caution in attributing a role of primary importance to a renal lesion simply because it is found in a patient who has hypertension. This study demonstrates that factors concerning the control of blood pressure which are inherent in each person may be of similar importance in the development of hypertension when there is an associated renal disease as in the development of hypertension when no renal disease is present. The presence or absence of these inherent factors may explain why hypertension develops in some patients who have a certain type of renal disease, whereas in other patients who have a similar type and extent of renal disease, hypertension does not develop.

AUTHORS.

Holman, Emile: Clinical and Experimental Observations on Arteriovenous Fistulae. Ann. Surg. 112: 840, 1940.

In the first 24 to 48 hours after the establishment of a large arteriovenous fistula, the heart diminishes in size, and is followed, if the animal survives, by a prompt return to normal, and, subsequently, by a gradual dilatation which may be apparent within 4 to 5 days.

Death due to an excessive diversion of blood through the fistula may occur, accompanied by a marked diminution in cardiac size.

The dilatation that accompanies an arteriovenous fistula is not restricted to the heart but affects the vessels involved in the fistulous circuit. The same cause is responsible for both dilatations, an increase in the volume or bulk of blood flowing through that part of the circulatory system through which the blood short-circuited by the fistula must flow; namely, all the chambers of the heart, the proximal artery, the fistula, and the proximal vein.

In the growing animal the dilatation and enlargement may be very great without evidence of decompensation and may be accompanied by pronounced hypertrophy. It is suggested that when dilatation outstrips hypertrophy, decompensation occurs; when dilatation is paralleled by a commensurate hypertrophy, great enlargement and dilatation of the heart may occur without decompensation.

In a crucial experiment involving three litter mates of equal weight and stature, one acting as control, one having an aorta vena cava fistula 12 mm. in circumference, and one having an aorta vena cava fistula 18 mm. in circumference, there occurred an increase in blood volume commensurate with the size of the fistula.

In the same animals an increase in the capacity of the circulatory system occurred also commensurate with the size of the fistula. The increase in capacity and the increase in blood volume closely paralleled each other.

In an animal with bilateral femoral fistulae the increase in blood pressure and reduction in pulse rate were greatest when both fistulae were closed simultaneously and considerably less when either fistula was closed separately. The physiologic effect of a fistula, therefore, clearly depends upon the volume of blood diverted through the fistula and, consequently, upon its size.

The transient high systolic and diastolic pressures that persist for several days following operative closure of a fistula are due to the increase in blood volume that has occurred during the existence of the fistula. The permanent elevation of diastolic pressure is secondary to the elimination of an area of decreased peripheral resistance.

In animals having bilateral femoral fistulae, vena-caval pressures were highest with both fistulae open, least with both fistulae closed, and intermediate pressures were obtained on closing one or the other fistula separately. Venous pressures proximal to a fistula are determined by the volume of blood diverted through the fistula and, therefore, by the size of the fistula.

AUTHOR.

Bigger, I. A.: The Surgical Treatment of Aneurysm of the Abdominal Aorta.
Ann. Surg. 112: 879, 1940.

An attempt has been made to collect the cases of aneurysm of the abdominal aorta and common iliac arteries treated by operations (excluding wiring) upon the aorta. The various surgical procedures which may be applicable to these aneurysms (excluding wiring) are discussed.

Two new cases are reported:

One patient, a poor surgical risk, developed left-sided heart failure with pulmonary edema and died following occlusion of the aorta proximal to the aneurysm.

A young man with a ruptured traumatic aneurysm had a preliminary occlusion of the aorta proximal to the aneurysm and one month later a restorative endoaneurysmorrhaphy. When examined one year after the endoaneurysmorrhaphy, the patient appeared to be well; there was no evidence of aneurysm, and the lumen of the aorta was obviously patent.

We realize that there is a marked difference between traumatic and spontaneous aneurysms and that the methods of treatment used in one may not be applicable in the other. For example, it is unlikely that one would find a spontaneous aortic aneurysm suitable for the type of operation, reconstructive endoaneurysmorrhaphy, used in our second case, but it seems likely that a small number of spontaneous aneurysms will be found suitable for obliterative endoaneurysmorrhaphy. Such operations probably should not be attempted unless the aneurysm arises distal to the renal arteries and, almost certainly, should not be attempted when the aorta is diffusely calcified. Proximal occlusion of the aorta should be undertaken as a pre-

liminary operation. This brings about shrinkage of the sac so that at the second operation either the aorta or the common iliac arteries may be ligated immediately distal to the aneurysm.

If the iliac arteries are permanently occluded, care should be taken to see that the ligatures are placed on the common iliacs, not the external iliacs, and the internal iliacs (hypogastrics) should be carefully protected because of their great importance as collateral channels.

Also, all vessels communicating with the sac should be ligated insofar as possible before the sac is opened. Only by the employment of meticulous preliminary preparation can one hope for success in such cases.

Aneurysms of the proximal portion of the abdominal aorta which have such essential arteries as the celiac, superior mesenteric, or both renals arising from the sac, probably should not be treated surgically, while in those aneurysms arising above the renal arteries but without any of the essential arteries originating from the sac proximal ligation may be justifiable.

AUTHOR.

Elkin, Daniel C.: Aneurysm of the Abdominal Aorta. Ann. Surg. 112: 895, 1940.

This report is concerned primarily with the effects of ligation of the abdominal aorta and consideration of those cases in which this procedure has been carried out. Therefore, the treatment of aortic aneurysm by other methods has not been considered. In only six patients upon whom ligation has been performed may the procedure be considered in any degree successful. Other means of treating an aneurysm of this vessel should be considered, but it is improbable that wiring, coagulation, or the application of the Matas principle of endoaneurysmorrhaphy could be carried out with any great hope of success. The effect upon the heart and circulation should be further studied, and methods of producing occlusion by other means than ligation must be developed before the operation can be successfully performed in the majority of cases.

AUTHOR.

Pearse, Herman E.: Experimental Studies on the Gradual Occlusion of Large Arteries. Ann. Surg. 112: 923, 1940.

Closure of the aorta both by intravascular thrombosis and by extravascular irritation has been demonstrated. It remains to perfect the methods by which this is done, for they can, in all probability, be improved.

AUTHOR.

Gage, Mims, and Ochsner, Alton: The Prevention of Ischemic Gangrene Following Surgical Operations Upon the Major Peripheral Arteries by Chemical Section of the Cervicodorsal and Lumbar Sympathetics. Ann. Surg. 112: 938, 1940.

We have employed the physiologic method, i.e., sympathetic block, of increasing the collateral circulation as a preliminary procedure to the ligation of major peripheral arteries in ten cases. In all but two of these cases, the collateral circulation was found to be inadequate by the Matas compressor test. In the other two cases, one of which was an aneurysm of the common iliac and the other a stab wound of the common femoral, the test could not be applied. Of these ten cases, one was a mycotic aneurysm of the right common iliac artery. Following sympathetic block and ligation of the common iliac at its origin, there was no change in color and no decrease in temperature of the corresponding extremity. There were two cases of arterial aneurysm of the femoral artery and three cases of popliteal aneurysm which

were cured by obliterative endoaneurysmorrhaphy. Three of the cases consisted of arteriovenous aneurysm, two of which were femoral and one of which was popliteal. These are treated by quadruple ligation. There was one case of stab wound of the common femoral which required ligation. In none of these cases of ligation of the major peripheral arteries treated by preliminary sympathetic block was there any evidence of ischemia or deficiency of the peripheral circulation.

We have also used sympathetic block in four cases of embolus of the femoral artery. In one case the embolus was removed after sympathetic block. The other three cases were not operated upon. In all these cases the classic clinical manifestations of arterial embolism were present. Following novocain block of the lumbar sympathetic ganglia and chain on the affected side, there was a loss of numbness and a return to normal of color and temperature of the extremity. In peripheral arterial embolism there is not only high incidence of ischemic gangrene, but also a high mortality, the gangrene increasing the mortality. Therefore, we believe that sympathetic block will not only materially decrease the incidence of ischemic gangrene but will also lower the immediate mortality.

AUTHORS.

Heinbecker, Peter: A Role for Surgeons in the Problem of Essential Hypertension. *Ann. Surg.* 112: 1101, 1940.

Essential hypertension results when there is narrowing of peripheral arterioles with a maintained cardiac output. The vascular narrowing, presumably, is effected by a renal pressor substance released during a state of renal asphyxia.

It is believed that the initiation of the renal arteriolar narrowing necessary to bring about the renal asphyxia may be effected by nervous or humoral influences.

Regardless of the manner of its initiation, the process can become self-perpetuating. Neither nervous nor endocrine influences need, thereafter, play an essential role.

It is regarded as highly probable that hypertension occurs particularly in persons whose blood vessels are so constituted that they respond hyperdynamically to vaso-pressor influences. If such pressor influences are present in abnormal amounts, even normal renal blood vessels may constrict sufficiently to initiate renal ischemia.

Experimental and clinical evidence is cited to show that continued functional narrowing of blood vessels leads to occlusive narrowing. The degenerative changes characteristic of the occlusive disease are presumed to follow interference with the function of the vasa vasorum.

Splanchnic section may be expected to relieve renal ischemia initiated by vaso-constrictor influences if the renal ischemia has not become self-perpetuating.

Evidence that epinephrine lowers the threshold for excitatory influences on the nervous system and increases the magnitude of the cortical response to identical peripheral stimuli is presented.

The symptomatic relief afforded by splanchnic section, in cases where there is no drop in blood pressure, is considered due to adrenal denervation.

Experimental evidence that a substance produced as a consequence of renal ischemia may increase in certain animals the tone of the smooth muscle of the iris and nictitating membrane is reported. Under such circumstances the effect of exogenous epinephrine on these structures is also enhanced.

Typical case records showing the effect of splanchnic section at various stages of hypertensive disease are presented.

A role for the surgeon in the solution of the problem of essential hypertension is to determine the number and types of cases in which nervous influences set into activity the mechanism by which hypertension is initiated. This can be done only if cases are treated in their initial stage.

AUTHOR.

Book Review

HYPERTENSION AND NEPHRITIS: By Arthur M. Fishberg, M.D., Associate in Medicine, Mt. Sinai Hospital, New York, Ed. 4, 1940, Lea and Febiger, Philadelphia, 779 pages, 41 illustrations, \$7.50.

During the rather short period which has elapsed since the appearance of the previous edition of Dr. Fishberg's book, a very large volume of new knowledge has been added to the subject of hypertension. Since this new knowledge is critically surveyed in the new edition, it is practically a new book. The subject is surveyed in its broadest aspects, and is discussed fully from the viewpoint of vascular function. Comprehensive and up-to-date discussions of chemical, physiologic, and pathologic aspects of hypertension are included. The rapidly growing and extensive literature dealing with recent experimental work is critically examined and admirably summarized. However, the purely practical phases of hypertension and nephritis are not neglected, but are maintained at the previous standard of excellence, as presented in the earlier editions.

Most books on clinical medicine tend to deal with the subject under discussion either from the standpoint of disease entities, or from the standpoint of symptoms. Dr. Fishberg uses both approaches. Beginning with a consideration of renal function, various manifestations of renal disease, such as uremia, edema, and albuminuria, are considered in painstaking detail. The several types of nephritis are then discussed in an unusually clear manner. The last portion of the book deals with hypertension, which is approached from all different points of view.

The more recent developments in these several fields have been thoroughly sifted by the author, and he has included references to most of the new work, as well as careful, critical summaries of the significance of such work. This difficult task in a field which is changing so rapidly has been performed in excellent fashion. Certainly no book in the English language can compare with this one in the field of hypertension and nephritis. Practicing physicians, medical students, and investigators will all join in hoping that Dr. Fishberg will continue to present from time to time new editions of his book, which is now generally accepted as a medical classic.

TINSLEY R. HARRISON.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. PAUL D. WHITE
President
DR. ROY W. SCOTT
Vice-President

DR. T. HOMER COFFEN
Treasurer
DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

*DR. EDGAR V. ALLEN	Rochester, Minn.	*DR. EDWIN P. MAYNARD, JR.	Brooklyn
DR. T. HOMER COFFEN	Portland, Ore.	*DR. THOMAS M. McMILLAN	Philadelphia
DR. CLARENCE DE LA CHAPELLE	New York City	DR. JONATHAN MEAKINS	Montreal
DR. WILLIAM DOCK	San Francisco	DR. E. STERLING NICHOL	Miami
DR. HUGH FARRIS, St. John, N. B., Canada		DR. FRANKLIN R. NUZUM	Santa Barbara
DR. NORMAN E. FREEMAN	Philadelphia	*DR. STEWART R. ROBERTS	Atlanta
DR. GEORGE R. HERRMANN	Galveston	DR. ROY W. SCOTT	Cleveland
DR. T. DUCKETT JONES	Boston	DR. FRED M. SMITH	Iowa City
*DR. WILLIAM J. KERR	San Francisco	*DR. HOWARD B. SPRAGUE	Boston
DR. EMANUEL LIBMAN	New York City	DR. WILLIAM D. STROUD	Philadelphia
DR. DREW LUTEN	St. Louis	*DR. PAUL D. WHITE	Boston
DR. GILBERT MARQUARDT	Chicago	DR. FRANK N. WILSON	Ann Arbor
*DR. H. M. MARVIN	New Haven	*DR. IRVING S. WRIGHT	New York City
		DR. WALLACE M. YATER	Washington, D. C.

DR. H. M. MARVIN, *Chairman, Executive Committee*
and *Acting Executive Secretary*

GERTRUDE P. WOOD, *Office Secretary*

TELEPHONE CIRCLE 5-8000

THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-seven physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$11.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

*Executive Committee.

The American Heart Journal

VOL. 22

AUGUST, 1941

No. 2

Original Communications

STUDIES ON CONGESTIVE HEART FAILURE

I. THE IMPORTANCE OF RESTRICTION OF SALT AS COMPARED TO WATER

HENRY A. SCHROEDER, M.D.
NEW YORK, N. Y.

THERE is fairly general agreement as to the importance of restricting fluids in the treatment of congestive heart failure, but in the matter of the restriction of sodium chloride, and to what extent it should be restricted, there is difference of opinion. Some textbooks¹ advocate rigid restriction of fluids. Osborne and Fishbein, and others,² advise restriction of both fluids and salt, although little investigation has been done to substantiate this advice. Various "cardiac diets" in general use are relatively poor in salt, and the limitation of fluids is widely practiced in the treatment of heart failure when edema is present. Although in normal man there may be an excess of tissue fluid after the ingestion of a large amount of salt, but not of water,³ it is uncertain whether salt, fluids, or both, are necessary factors in the occurrence or prevention of the edema of heart failure. An attempt has been made, therefore, to learn the importance of each of these substances.

Twenty-three patients were selected for study, and an attempt was made to find the most obstinate cases of congestive heart failure. Patients were given weighed diets, in which the content of sodium chloride (calculated from Sherman's tables⁴) the caloric value, the protein content, and the intake of fluid were constant for definite periods.* The amount of activity to which the patient had been accustomed prior to study was not changed, so that spontaneous diuresis as a result of rest might be avoided. Digitalis was given when auricular fibrillation with a rapid ventricular rate was present, or when the patient had previously

From the Hospital of the Rockefeller Institute for Medical Research, New York.

Read before the American Heart Association, May 13, 1939, St. Louis, Mo.

Received for publication Oct. 21, 1940.

*The value of the diets used was usually 2,000 calories (in order to prevent change in weight from loss of body substance), although occasionally 1,500 calories were given. The protein content was as high as was consistent with the amount of salt, i.e., 70-80 Gm. in a diet containing 1.0 Gm. of NaCl. or 35-40 Gm. in one containing 0.5 Gm. The amount of water in the food was calculated, and was found to vary but little; it was not included in the total intake of fluids shown in the charts. Unless previously under prolonged observation, the patients were usually observed in the hospital for two weeks on a standard regime, without changes being made, before they were studied.

been taking it. Diuretic drugs were administered only when the condition of the patient necessitated their use. The output of chloride in the urine was measured daily (Volhard-Arnold method).

The Action of Sodium Chloride.—It was observed in all cases that a reduction in the amount of ingested salt was followed by a loss in weight and in edema fluid (Table I). Often diuresis and loss of weight began immediately when the intake of sodium chloride was reduced from 2.0 Gm. in twenty-four hours to 1.0 Gm.* In obstinate cases in which the edema was of long standing, it was always possible to prevent the accumulation of fluid by restriction of salt, although occasionally this necessitated a diet containing as little as 0.5 Gm. in twenty-four hours.

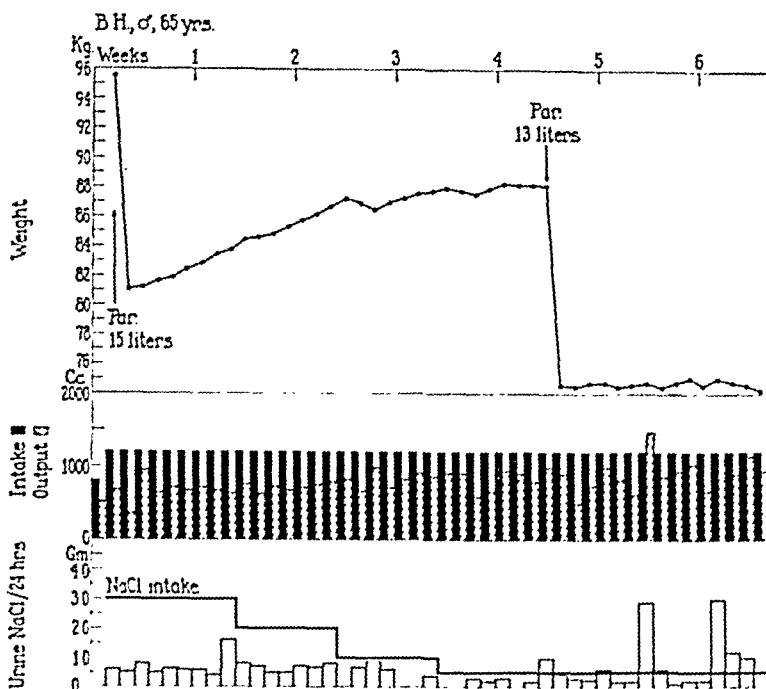


Fig. 1.—Case 8. B. H., aged 65, suffered from heart failure for three years after an attack of coronary occlusion. There was an enormous ascites; paracentesis had to be done twenty-nine times. Digitalis, mercurial diuretics, ammonium chloride, and various other measures had been of no avail. Auricular fibrillation, with a slow ventricular rate, was present. There was edema in dependent tissues. At "Par," 15 liters were removed from the abdomen. Following this, on an intake of 3.0 Gm. of NaCl, he gained 471 Gm. a day; on 2.0 Gm., 386 Gm. a day; on 1.0 Gm., 114 Gm. a day; on 0.5 Gm., 29 Gm. a day. Thirteen liters were then removed from the abdomen, and his weight remained constant for six weeks. He became free of edema after various diuretics had been given; his body weight was 60 kg. Edema could then be controlled by a diet containing 1.0 Gm. of NaCl. Edema recurred slowly after discharge from the hospital. The diet contained 0.5 Gm. NaCl, to which extra salt was added during the first three weeks. He was ambulatory during the period of observation.

The addition of a small amount of salt to the diet (1.0 Gm. to 2.0 Gm.) was followed, on the other hand, by an immediate gain in weight. By changing the quantity of salt in the diet, without varying the food, the intake of fluids, or the patient's activity, the weight and the amount of

*The amount of sodium chloride in the diet was calculated exactly, according to the tables of Sherman. It is probable that foods obtained from different sources and localities may vary in their content of sodium chloride, and that these figures may not be accurate. Foods were, therefore, obtained from the same sources insofar as possible, and these amounts of sodium chloride are probably constant. When patients refused part of their diet it was subsequently given to them in other forms, in order that the total intake per day should remain constant.

edema could be controlled at will. That a reduction in the intake of salt will result in lessening of the accumulation of edema in obstinate cases of congestive heart failure can be demonstrated (Fig. 1).

The Action of Fluids.—It was found that the intake of fluids had little relation to the accumulation or disappearance of edema when the intake of salt was low enough. Weight was gained more rapidly in an occasional case when salt was not severely restricted and the intake of fluids forced (Fig. 2B), but, on the administration of a minimal amount of sodium chloride, weight was lost and edema disappeared as rapidly on a regime of restriction of fluids as on one in which water was freely given (Table II). There was, in fact, no effect on varying the intake of fluids even in cases of severe chronic congestive heart failure (Fig. 2, A and B). In only two cases was a sudden increase in the intake of fluids followed by a gain in weight and failure of the output of urine to increase.

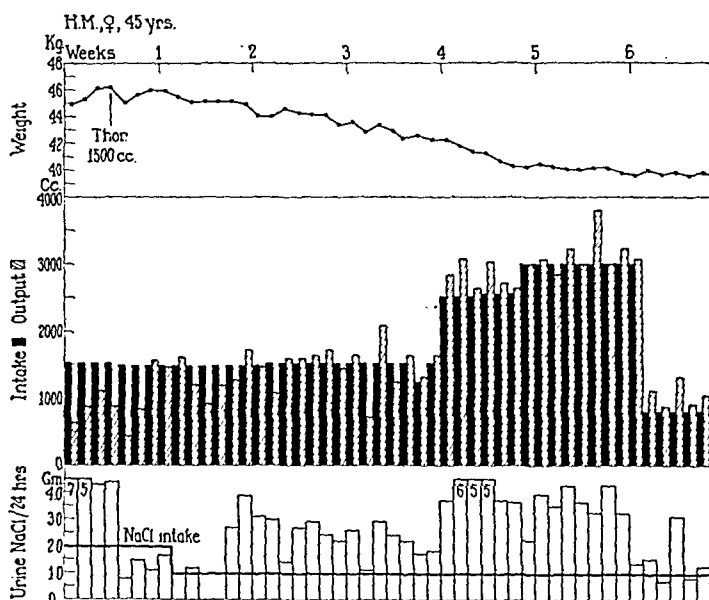


Fig. 2.—A, Case 16. H. M., a woman aged 45, had suffered from chronic congestive heart failure for six years; her first attack of cardiac failure occurred after she was 34. She had acute rheumatic fever at 18. For four years she had been bed-ridden because of continuous edema, ascites, and hydrothorax. Mercurial diuretics, squills, and digitalis had not controlled her heart failure, and she had rarely been free of edema. There were signs of involvement of the mitral, tricuspid, and aortic valves, and auricular fibrillation, requiring the use of digitalis, was present. She was given a diet containing 1.0 Gm. of NaCl, to which extra salt was added as needed.* On an intake of 2.0 Gm., in spite of the removal of 1.5 liters of fluid from her chest there was a slight gain in weight. On 1.0 Gm. there was an immediate loss, which continued. When the fluid intake was increased from 1500 c.c. a day to 2500, slight diuresis occurred. It was then increased to 3000. She was free of edema, but there remained a moderate amount of fluid in the chest. Reduction of the intake of fluid to 800 c.c. a day resulted in no further loss of weight.

*The rather high excretion of chlorides during the first four days probably represents ammonium chloride which the patient had been taking.

Both patients exhibited marked diminution of renal function. But in every other case without organic renal disease, under these conditions the amount of water ingested did not affect the course of the illness (Fig. 3), with the exception of a few instances in which its limitation appeared

sometimes to result in an adverse change in the weight curve (Cases 16, 17, 18, 19).

The Choice of a Diet.—In most instances 1.0 Gm. of sodium chloride in the diet was found to be low enough to prevent edema, but in a few cases, in which the heart failure was of long duration and the edema continuous, it was necessary to reduce the intake of salt to 0.5 Gm. per day. By measuring the excretion of chlorides in the urine it was possible to estimate the degree of restriction of sodium chloride which would be necessary for an effect, and a diet containing less than the amount excreted was used. Patients for whom 1.0 Gm. of salt per day was too much were sometimes able to tolerate that amount when compensation had been restored on a smaller intake (of salt).

A diet containing 0.5 Gm. of sodium chloride per day is inadequate in its protein content and cannot be given for a long period of time. A diet in which the salt content is 1.0 Gm. is adequate except for vitamins, and these should be added. Samples of the diets employed are shown (Table III).

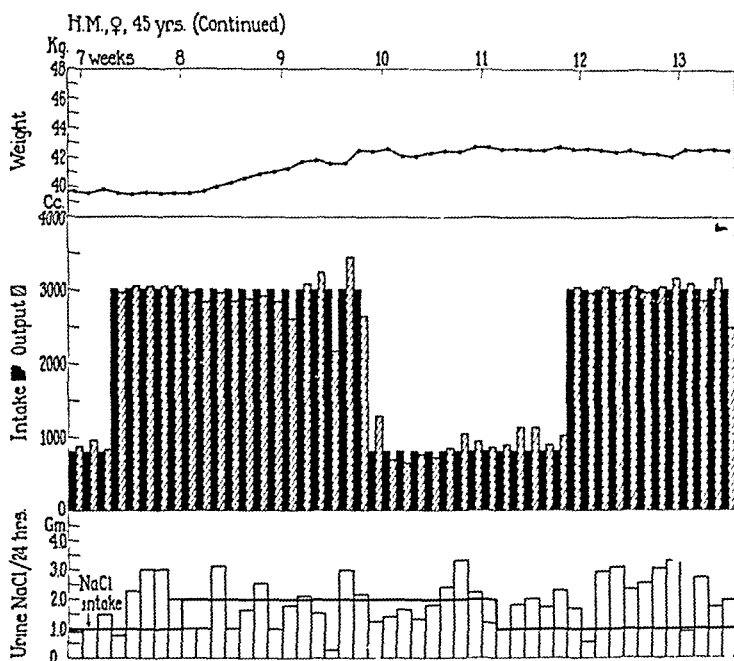


Fig. 2.—B, Same patient, continued. The intake of fluids was suddenly increased from 800 c.c. to 3000 c.c. a day without change in body weight. However, when 1.0 Gm. of NaCl was added to the diet a slow gain in weight resulted; this was accompanied by dyspnea, discomfort, and recurrence of edema. Reduction in the intake of fluids to 800 c.c. a day was immediately followed by a slight loss of weight for one day, but the gain continued, although more slowly. When the extra salt was removed from the diet the weight again became constant, and, when the intake of fluids was increased to 3000 c.c. a day, a slight loss resulted. This patient remained free of edema for five months under observation in the hospital, and for four months at home. She was unable to keep to her diet for three weeks, took considerable extra salt, and immediately suffered a recurrence of congestive heart failure and died. At autopsy, marked rheumatic involvement of the mitral, tricuspid, and aortic valves was found. The patient was in bed during the period of observation.

Disturbances Associated With a High Intake of Fluids.—In two cases, already mentioned, in which there was a diminution of renal function, with retention of nitrogen in the blood and severe disease of the liver, the rapid increase in the intake of fluids was accompanied by no increase

in the output of urine for several days. These patients complained of weakness, prostration, muscular cramps, and drowsiness, and gained weight rapidly. The chlorides of the plasma in one case were found to be markedly diminished; in the other no measurements were made. When the intake of fluids was subsequently reduced, diuresis occurred and weight was lost. It was believed that these symptoms represented "water intoxication," that is, dilution of electrolytes caused by failure to excrete ingested water. When renal function was normal a rapid increase in the intake of fluids was accompanied by an increase in the output of urine. Patients who were suffering from attacks of paroxysmal dyspnea or pulmonary edema did not have an increase in the number of attacks when the intake of fluids was high.

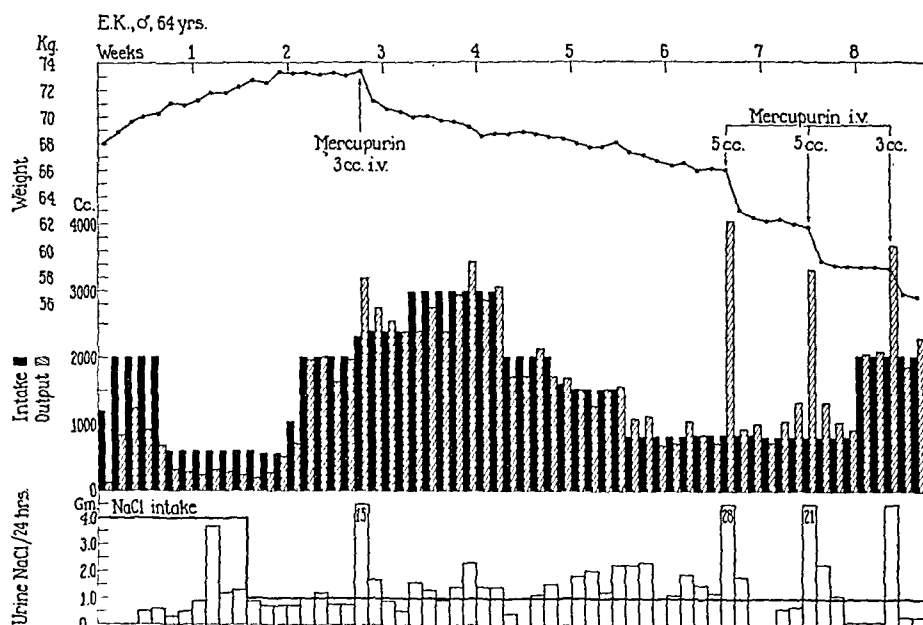


Fig. 3.—Case 18. E. K., a man, aged 64, had suffered from chronic congestive heart failure for fifteen years, and had been continually edematous for six years while under observation; he required 4 to 6 c.c. of mercupurin or salyrgan every two to three weeks. There were marked edema in dependent tissues and moderate ascites. He was given a diet containing 1.0 Gm. of NaCl, to which extra salt was added. On 4.0 Gm. of NaCl and 2000 c.c. of fluid a day, his gain in weight was rapid, and it continued, although less rapidly, when the intake of fluids was 600 c.c. a day. Even after reducing the amount of NaCl to 1.0 Gm., there was a slight gain, but an increase in the intake of fluids to 2000 c.c. a day resulted in no further change. Because of discomfort, 3.0 c.c. of mercupurin (half his usual dose) were given intravenously, and this initiated diuresis. This did not appear to be influenced by the amount of fluids ingested, but continued at the same rate whether 3000 c.c. or 800 c.c. a day were given. The sudden increase again from 800 c.c. to 2000 c.c. a day resulted in no change in weight. The patient subsequently died of cerebral hemorrhage. He was ambulatory during the period of observation.

DISCUSSION

Water may act as a diuretic, and salt and water as an antidiuretic. Peters⁵ describes the mechanism in these words: "Presumably, when water alone is given, the concentration of water in the serum is increased, and that of salt diminished to such an extent that the kidneys are stimulated to excrete more than the usual amount of water. . . . The adminis-

TABLE I
EFFECT OF INTAKE OF SODIUM CHLORIDE ON THE WEIGHT OF PATIENTS WITH CONGESTIVE HEART FAILURE

CASE NO.	NAME & SEX	AGE YR.	DURATION HEART FAILURE MONTHS	SIGNS OF HEART FAILURE*				NaCl. INTAKE† GM./DAY	FLUID INTAKE C.C./DAY	NO. DAYS OBSERVATION	WEIGHT CHANGE KG.	AVERAGE WEIGHT CHANGE GM./DAY	REMARKS
				EDEMA	ASCITES	HYDRO-THORAX							
1	E. H. ♂	73	2	++	0	0		(5)	1500	21	-0.4	-19	Arteriosclerotic heart disease. Complete heart block.
				++	0	0		(2)	1500	7	-1.0	-143	
2	E. H. ♀	89	2	0	0	0		ad lib.	ad lib.	23	-4.0	-174	
3	M. C. ♀	64	12	0	0	0		(2)	ad lib.	9	+3.0	+333	
				+	0	0		(2)	ad lib.	11	-1.5	-136	
4	R. G. ♂	56	2	++	0	0		ad lib.	1500	20	+5.0	+250	Arteriosclerotic heart disease. Mild congestive heart failure.
				+	0	0		(3)	2000	46	-3.0	-65	
5	M. W. ♂	62	3	++	0	0		(2)	2000	9	-3.2	-356	
				+	0	0		(2)	1500	7	-2.6	-371	
				++	0	0		(4)	1400	15	-3.2	-213	Arteriosclerotic heart disease. Pulmonary emphysema. Aortic stenosis.
				++	0	0		(2)	1400	20	+3.6	+180	
				0	0	0		(4)	1200	12	-7.2	-600	
				0	0	0		(2)	1200	4	+1.0	+250	
				0	0	0		(3)	1200	11	-1.3	-164	Hypertension. Slight renal insufficiency.
				0	0	0		1	1200	11	-1.1	-100	
				0	0	0			1200	11	-2.9	-264	
				0	0	0							
6	J. B. ♂	68	18	++	0	0							Arteriosclerotic heart disease.

*Signs of heart failure, i.e., at end of period.
†NaCl intake per day. Where indicated by (), the actual content of sodium chloride in the diet was not calculated daily but was estimated from sample diets, and is, therefore, approximate. When not so indicated, the content was calculated daily and was constant during the period of observation.

Arteriosclerotic heart disease.
Complete heart block.

Arteriosclerotic heart disease.
Mild congestive heart failure.

Arteriosclerotic heart disease.
Pulmonary emphysema. Aortic stenosis.

Hypertension. Slight renal insufficiency.

Arteriosclerotic heart disease.

Arteriosclerotic heart disease.

7	P. O. ♂	65	12	++ ++ ++ 0 ++ ++ 0 0	0	0	(2) 1 (2) 0.5 1 ad lib. 1	1200 1200 800 800 1800 1800 1800 1800	10 11 8 9 12 10 10 10	+1.2 -3.8 -0.5 -0.5 -2.3 -4.0 +1.0 -1.5	+120 -345 -63 -256 -333 +100 -150	Complete heart block. Syphilis. Arteriosclerosis.
8	B. H. ♂	65	36	++ ++ +++ +++ +++ +++ ++	++ +++ +++ +++ +++ ++	0 0 0 0 0 0	3 2 1 0.5	1200 1200 1200 1200 1200 1200	7 7 7 7 14	+3.3 +2.7 +0.8 +0.2 0	+471 +386 +114 +29 0	Arteriosclerotic heart disease. Auricular fibrillation, slow ven- tricular rate.
9	H. P. ♂	47	1	+++ ++	0 0	+ +	3.0 1.0	1500 1500	8 7	+0.6 -1.3	+75 -186	Arteriosclerotic heart disease. Old coronary occlusion.
10	L. S. ♀	41	2	++ +	0 0	+ 0	3.0 1.0	1500 1500	7 10	0 -5.0	0 -500	Rheumatic heart disease. Mi- tral stenosis. Tricuspid in- sufficiency. Auricular fibril- lation.
11	M. K. ♀	49		0 + 0	0 0 0	0 0 0	(2) (4) (2)	2000 2000 2000	10 7 10	-0.3 +2.6 -2.1	-30 +371 -210	Rheumatic heart disease. Mi- tral stenosis. Auricular fibrillation. Incipient heart failure.

TABLE II

	+ + +		
	+ + +		
*Signs of heart failure, i.e., at end of period.			
†NaCl intake per day. Where indicated by ()			
from sample diets, and is, therefore, approximate.			
observation,			

*Signs of heart failure, i.e., at end of period.	
†NaCl intake per day. Where indicated by () observation,	+ + + + + + +

18	E. K. ♂	64	18	++ ++ ++ ++	++ ++ ++ ++	0	4	2000	4	+1.3 +2.6 +0.5 -0.2 -0.3 -1.3 -1.3 -0.3 -1.1	+325 +433 +125 -50 -433 -186 -60 -137	Arteriosclerotic heart disease
19	M. J. ♀	44	12	++ ++ ++ ++ ++ ++ ++	++ ++ ++ ++ ++ ++ ++	0 0 0 0 0 0 0	1 1 1 0.5 1 1 1	1200 2400 3000 3000 2000 2000 800	9 9 3 5 5 5 8	-1.2 -0.1 +0.2 -0.3 -1.6 +0.3	-133 -11 +67 -60 -320 +60	Hypertension Long-standing heart failure Arteriosclerosis Auricular fibrillation
20	W. H. ♂	58	1	++ ++ ++ ++ ++ ++ ++	++ ++ ++ ++ ++ ++ ++	++ ++ ++ ++ ++ ++ +	1 1 1 1 1 1	1200 1800 600 600 600 1200	13 7 9 9 9 5	-1.2 +0.8 -0.6 +0.3 +0.8	-923 +114 -67 +33 +160	Arteriosclerotic heart disease Old coronary occlusion
21	E. H. ♀	69	6 mo.	++	++	+++	1 1	1500 2000	11 7	-1.3 +0.5	-118 +71	Arteriosclerotic heart disease
22	C. M. ♂	11	18 mo.	++++	+++	0	1 1	1200 700	5 11	-0.1 -1.3	-20 -118	Acute rheumatic fever Mitral and tricuspid insufficiency and stenosis
23	F. R. ♀	48	2	+++ ++ +	0 0 0	0 0 0	1 1 1	800 2000 1500	6 8 8	-3.1 -2.2 -1.0	-602 -275 -125	Hypertension. Obesity Pituitary dyscrasia (?)
4	R. G. ♂	56	3 mo.	+ 0	0 0	0 0	(2) (2)	1400 2000	21 29	+3.1 +3.1	+148 +107	Hypertension, with slight renal insufficiency
7	P. O. ♂	66	3 mo.	++ ++ ++	0 0 0	± ± ±	1 1 1	1000 3000 1000	12 5 6	+0.8 +3.2 0	+67 +604 0	Arteriosclerosis. Syphilis Complete heart block Urea clearance 20 per cent
8	B. H. ♂	65	3	++	++	++	0.5 0.5 0.5	1200 2500 1200	7 4 5	+0.1 +3.5 -2.5	+14 +875 -500	Arteriosclerotic heart disease Old coronary occlusion Urea clearance 25 per cent

TABLE III
SAMPLE DIET CONTAINING 2,000 CALORIES AND 0.5 GM. NaCl

	FOOD (grams)	PROTEIN (grams)	NaCl (mg.)	CALORIES
<i>Breakfast</i>				
Bread	45	4.2	34	116
Butter	12	0.1	2	87
Jelly	20	0.1	7	48
Cream	40	0.9	31	153
Sugar	12	--	--	48
Canned apricots	50	0.5	49	37
Cream of wheat	120	1.3	2	44
<i>Dinner</i>				
Steak (sirloin)	45	9.9	107	52
{ Rice	25	2.0	16	88
{ Butter	10	0.1	2	73
{ Fresh string beans	75	1.8	35	32
{ Butter	5	0.1	1	37
{ Apple, raw (sauce)	100	0.4	28	63
{ Sugar	10	--	--	40
{ Whipped cream	20	0.4	15	76
{ Lemon juice	20	--	3	8
{ Lactose (drink)	40	--	--	160
<i>Supper</i>				
{ Bread	45	4.2	34	116
{ Butter	12	0.1	2	87
{ Jelly	20	0.1	7	48
{ Steamed Irish potato	90	1.8	50	77
{ Butter	10	0.1	2	73
{ Lettuce	20	0.2	10	3
{ Pot cheese	25	5.2	--	28
{ Fresh tomato	50	0.5	16	12
{ Olive oil	15	--	--	135
{ Canned cherries	75	0.8	44	67
Candy	55	0.1	4	194
	1,066	34.9	501	2,002

tration of normal saline provokes the kidneys to no extra activity, because it does not appreciably alter the composition of the serum." Adolph⁶ analyzes the actions of salt and water as follows: "If water is drunk, an equal amount is excreted usually within two or three hours in the urine, in addition to the water excreted at the normal rate. Meanwhile, the insensible loss of water increases in rate so that the body often ends up by having as little or less water than it would have had if none had been ingested. The same result is obtained from drinking a solution of almost any salt in a concentration that is osmolar with the blood. But if the salt is sodium chloride or sodium bicarbonate, then little or no diuresis results and the excess fluid is eliminated very slowly (during twenty-four to forty-eight hours)." According to Peters and Van Slyke,⁷ "Retention of base entails retention of water, and accumulation of water is associated with storage of base. When the water changes affect chiefly the extracellular fluids, the base simultaneously retained or lost is chiefly sodium."

Therefore, there is good reason for rigid restriction of sodium chloride in chronic congestive heart failure. Edema fluid is composed principally of water and salt.⁷ Considerable water is necessary in the economy of

TABLE III—CONT'D
SAMPLE DIET CONTAINING 2,000 CALORIES AND 1.0 GM. NaCl

	FOOD	PROTEIN	NaCl	CALORIES
	(grams)	(grams)	(mg.)	
<i>Breakfast</i>				
{Bread	40	3.7	30	104
{Butter	12	0.1	2	87
{Jelly	15	--	5	35
{Cream	40	0.9	31	153
Sugar	15	--	--	60
Canned apricots	50	0.5	49	37
Cream of wheat	120	1.3	2	44
Egg (boiled)	50	6.6	179	80
<i>Dinner</i>				
{Bread	40	3.7	30	104
{Butter	12	0.1	2	87
{Jelly	15	--	5	35
{Steak (sirloin)	90	19.9	213	105
Rice	20	1.6	13	71
Butter	15	0.2	3	111
{Fresh string beans	75	1.8	35	32
{Butter	4	--	--	29
{Apple, raw (sauce)	95	0.4	27	60
Sugar	10	--	--	40
Whipped cream	25	0.6	19	96
<i>Supper</i>				
{Bread	40	3.7	30	104
{Butter	12	0.1	2	87
{Jelly	15	--	5	35
{Roast turkey	60	19.0	203	97
{Steamed Irish potato	75	1.5	42	64
Butter	12	0.1	2	87
{Lettuce	20	0.2	10	3
{Fresh tomato	50	0.5	16	12
{Pot cheese	25	5.2	--	28
{Olive oil	5	--	--	45
{Canned cherries	75	0.8	44	67
	1,132	72.5	999	1,999

the organism, but excess salt is not. Water cannot be deposited in the tissue spaces without salt. Salt is, therefore, necessary for the formation of this type of edema.

The rationale for the rigid restriction of fluids is not clear. If the intake of water is limited and the patient dehydrated, the deposition of edema should be lessened. Although dehydration can result from this procedure, it is uncertain that diuresis is thereby initiated. In these cases the output of urine was markedly depressed when the intake of fluids was low, and diuresis was not established until an adequate amount of fluid was administered. Furthermore, if edema can be prevented by the restriction of water, that substance must be rigidly restricted, but this cannot be continued for long without serious consequences. The free water contained in a diet of 2,000 calories may amount to a liter or more, and the "water of metabolism" to an additional 200 c.c. Limitation of this water necessitates a limitation of food which may, for short periods, be practicable, but obviously not for prolonged treatment. A certain volume of urine is necessary, furthermore, for the optimum excretion of chlorides (approximately 60 c.c. per hour). If the volume is permitted

to shrink below this the output of chlorides is lessened.⁸ The opposite course is, therefore, preferable. If the output of urine can be increased by the administration of water, accompanied by rigid restriction of salt, the depletion of chlorides would be accelerated. On this plan, in no case did the output of urine fail to increase when extra water was added. Sometimes an increase in the amount of water taken actually initiated increased excretion of chlorides, which was accompanied by loss of weight. Conversely, the oliguria which accompanied severe restriction of fluids was associated with a decreased excretion of chlorides in the urine.

It is evident from these data that the administration of comparatively large amounts of fluid to cardiac patients does not increase the rate of formation of edema, provided the intake of salt is low enough. Under these conditions, Newburgh⁹ and Schemm¹⁰ have given cardiac patients considerable volumes of water without observing deleterious results. It is likely, therefore, that restriction of only one of the components of edema fluid is necessary for the control of anasarca. Limitation of the ingestion of salt, including limitation of those foods in which the salt content is high, imposes little hardship upon the patient, whereas restriction of fluids to the degree necessary to produce an effect may be difficult, hazardous, and uncomfortable. The occasional diuresis, with loss of weight, which has been observed when fluids were given suggests that sometimes water is beneficial in this condition. For practical purposes it appears wise to allow patients with heart failure to drink as much water as they please, provided the intake of sodium chloride (and other sodium salts) is carefully limited.

Compared to the amount of salt in the diets used in this study, the amount in the usual "salt-free" or "cardiac" diet is relatively high. An ordinary ward diet to which no extra salt and no salty foods have been added contains approximately 4.0 Gm. of sodium chloride; one cooked without salt contains 2.0 to 3.0 Gm. One gram of salt is present, for example, in an average serving of lamb, beets, and carrots, or in 800 c.c. of milk. When attention is not paid to the kind of food, as well as to the amount, the salt content may mount with surprisingly rapidity. Since it has been shown that some patients may gain weight when taking 2.0 Gm. and remain at the same weight when taking 1.0 Gm. of salt in twenty-four hours, the kind of food given in the treatment of this type of edema assumes importance. The beneficial effects of the Karell diet (800 c.c. of milk in twenty-four hours) may be due to the low content of fluid and of food, but especially to the fact that the salt content is also reduced to 1.0 Gm.

Few complaints were made about these diets when the food was properly seasoned. Patients were able to take them at home with less hardship than would be caused by the restriction of fluids.

This method for the control of edema merely removes or limits at the source one of the factors which is responsible for the accumulation of

extracellular fluid. The usual measures must also be employed to promote diuresis and to prevent reaccumulation of edema. But edema in congestive heart failure may often be kept in abeyance for considerable periods by rigid restriction of the amount of sodium chloride in the diet.

SUMMARY

1. Twenty-three patients who were suffering from congestive heart failure were studied with a view to learning the relative importance of sodium chloride and water with respect to the accumulation and disappearance of edema.

2. The restriction of salt to a level below the output in the urine always resulted in a decrease in the amount of edema. Usually, a diet containing as little as 1.0 Gm. of salt in twenty-four hours was sufficient to cause diuresis or a cessation in the accumulation of edema, but the salt content of the ordinary "salt-free" diet was not low enough.

3. When the intake of salt was sufficiently restricted, the amount of fluid taken did not usually affect the edema.

4. Occasionally diuresis was observed to increase when the patient was taking plenty of fluids, and to decrease when fluids were rigidly restricted.

5. When renal insufficiency accompanied heart failure, a high intake of fluids resulted in symptoms similar to those of "water intoxication."

6. These studies suggest that restriction of salt is important in the control of the edema of congestive heart failure, but that the restriction of fluids is of little value.

REFERENCES

1. Mackenzie, J.: *Diseases of the Heart*, Ed. 3, London, 1913, Oxford University Press.
- Lewis, T.: *Diseases of the Heart*, New York, 1936, The Macmillan Co.
- White, P. D.: *Heart Disease*, New York, 1935, The Macmillan Co.
2. Fishberg, A. M.: *Heart Failure*, New York, 1937, The Macmillan Co.
- Harrison, T. R.: *Failure of the Circulation*, Baltimore, 1935, Williams and Wilkins Co.
- Osborne, D. T., and Fishbein, M.: *The Handbook of Therapy*, Ed. 9, Chicago, 1933, American Medical Association.
3. Baird, M. M., and Haldane, G. B. S.: Salt and Water Elimination in Man, *J. Physiol.* 56: 259, 1922.
4. Sherman, H. C.: *Chemistry of Food and Nutrition*, Ed. 5, New York, 1938, The Macmillan Co.
5. Peters, J. P.: *Body Water: The Exchange of Fluids in Man*, Springfield, Ill., 1935, C. C Thomas.
6. Adolph, E. F.: The Metabolism and Distribution of Water in Body and Tissues, *Physiol. Rev.* 13: 336, 1933.
7. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Vol. I. Interpretations, p. 753, Baltimore, 1931, Williams and Wilkins Co.
8. Marshall, E. K., Jr.: The Influence of Diuresis on the Elimination of Urea, Creatinine and Chlorides, *J. Pharm. Exper. Therap.* 16: 161, 1921.
9. Newburgh, L. H.: Personal communication.
10. Schemm, F. R.: Personal communication.

THE PRODUCTION AND STUDY OF CARDIAC FAILURE IN THIAMIN-DEFICIENT DOGS

ROY L. SWANK, M.D., RENO R. PORTER, M.D., AND
ANDREW YEOMANS, M.D.
BOSTON, MASS.

ALTHOUGH recent studies indicate that cardiac failure may be produced in man by a deficiency of vitamin B₁,¹⁻⁸ the experimental production and study of this condition in animals has apparently been undertaken by few investigators. McCarrison⁹ and Findlay¹⁰ noted hydropericardium in many of their vitamin B₁-deficient pigeons, and studies on thiamin-deficient pigeons¹¹ and rats¹² have shown that the electrocardiograms become abnormal. These and many other similar investigations¹³⁻¹⁶ have revealed bradycardia. However, other studies¹⁷⁻¹⁹ have indicated that the bradycardia was the result, in large part, of starvation.*

In a recent study²⁰ it was found that, in thiamin-deficient dogs, tachycardia and abnormal electrocardiograms frequently appeared. These dogs became very markedly emaciated and had severe paralysis, both flaccid and spastic. At their post-mortem examinations²¹ the right auricle and ventricle were found to be dilated, and the left ventricle in apparent contraction. Histologic examination of the myocardium revealed edema, perinuclear vacuolization, increase in the longitudinal striations, decrease in the cross striations, and hyalinization of many cardiac muscle fibers, and, in places, marked interstitial cellular infiltration was noted. In no instance was cardiac failure observed.

Another study, on pigeons,²² has shown that hydropericardium, edema and engorgement of the lungs, engorgement of the liver, and peripheral edema can be produced in a large percentage of the birds by feeding them a diet partially deficient in thiamin, provided the caloric intake is sufficient to prevent a significant loss of weight. These pigeons developed tachycardia and abnormal electrocardiograms, and histologic study of the myocardium revealed scattered areas of focal necrosis.

To ascertain whether these phenomena are in fact due to failure of the myocardium, we have produced a similar state in the dog for more detailed studies. The method by which cardiac failure was produced in six dogs by feeding them a diet deficient in thiamin, together with pathologic observations, will be presented in the present paper. Physiologic ob-

From the Departments of Medicine and Pathology, Harvard Medical School, and the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

Received for publication Oct. 9, 1940.

*We wish to take this opportunity to thank Dr. C. S. Burwell for many helpful suggestions during this investigation.

servations, using methods to be described separately,²³ will be presented as well, but in smaller numbers, because the symptoms of cardiac failure were followed so soon by death that few such studies were possible.

MATERIALS AND METHODS

Young, normal, adult, female dogs were used. They were individually caged and fed the following experimental diet, which is deficient in thiamin:

Casein (crude)	180.
Cod liver oil	40.
Peanut oil	40.
Corn starch	620.
Salt mixture	20.
Autoclaved yeast	50.

This diet (15 to 18 Gm. per kilogram of body weight) was consumed voluntarily for ten to fourteen days, but thereafter, because of anorexia, was mixed with an equal weight of water and introduced into the dog's stomach by tube. Supplemental feedings of thiamin (betabione, Merck) were given either intramuscularly or orally with the day's ration. Many dogs vomited; two dogs which retained most of each day's ration were given only small daily supplements of thiamin (25 micrograms), and were allowed to develop acute thiamin deficiency. Ten others were made chronically deficient in thiamin, as follows: After a preliminary, rapid depletion period of approximately ten to fourteen days, during which no thiamin was added to the day's ration, each dog vomited. When this had occurred on two successive days, 0.3 to 0.6 microgram of thiamin per gram of the experimental diet (depending upon how much was needed to prevent a recurrence of vomiting) was added to the daily ration (preferably), or given intramuscularly. This regimen was followed for a period of four to twelve weeks, during which time the thiamin stored in the body was slowly used up. In some instances the administration of thiamin was then discontinued or the dose was reduced to approximately 0.2 microgram per gram of experimental diet, in which cases signs of cardiac failure or death usually appeared within three to five days. In others in which the reduction in thiamin was less marked (to 0.4 microgram per gram of diet), the symptoms of failure appeared less acutely, or, for reasons to be discussed later, failed to appear.

For the purpose of control, two dogs were starved by giving them approximately 7 Gm. of the experimental diet per kilogram of their original weight, plus an intramuscular injection of 100 micrograms of thiamin each day. These dogs lost approximately 30 per cent of their original weight, but showed no evidences of thiamin deficiency (anorexia, paresis, or dyspnea). No further mention of these experiments will be made. Two other dogs were utilized to ascertain the amount of thiamin necessary to prevent vomiting or other signs of thiamin deficiency in chronically deficient animals.

RESULTS

Acutely Deficient Dogs.—Dogs 4 and 5 became deficient acutely. They vomited after consuming the experimental diet for twelve and seven days, respectively, and thereafter, to prevent further vomiting, received 25 micrograms of thiamin intramuscularly each day. Ataxia became apparent on the twenty-fourth and nineteenth days, respectively, when both dogs had lost 12 per cent of their original weight. One day later Dog 5 was found to have opisthotonus and extensor rigidity of the ex-

tremities. This was relieved in less than one hour by an intramuscular injection of 200 micrograms of thiamin.

In these and other (chronically deficient) dogs, ataxia was noticed first in the hind legs, later in the forelegs. It was characterized by a wide or straddle gait, misplacing of the feet, staggering, and a marked tendency to walk on the dorsum of the paws. Unless adequate amounts of thiamin were administered or the food intake greatly reduced, the ataxia became very much worse, a variable amount of spasticity of the extremities appeared, and in a few days there ensued a paralysis which was so severe that the animals were unable to stand or walk. This severe paralysis was due no doubt to motor as well as to sensory (proprioceptive) impairment, for the animals were unable to support their own weight. In a few cases the muscles of the neck also became involved, and the animals had difficulty in holding up their heads. Mild ataxia was abolished in seven to fourteen days by thiamin, but no attempt was made to restore to normal a dog that had severe paralysis. No evidences of cardiac failure were observed in the two acutely deficient dogs, and, as will be shown, paralysis (also starvation) tended to prevent the appearance of cardiac failure in the chronically deficient dogs. A similar observation on human patients was made by Keefer.³

Chronically Deficient Dogs.—(a) *General Consideration:* On the dietary regimen, which was partially deficient in thiamin, seven dogs developed sudden cardiac failure, principally of the left ventricle, and five of them died in a very few hours. Two of these were observed a short time before they died and showed labored breathing (not panting), pulmonary râles, cyanosis of mucous membranes, and poorly filled peripheral veins (as judged by the difficulty with which they were entered for the purpose of withdrawing blood). The other three were found dead in their cages. In no instance was dependent edema or an increase in peripheral venous pressure due to cardiac failure noted; all evidences pointed to failure of the *left* ventricle. Three of the dogs with cardiac failure developed mild ataxia very early in the experiment and were restored nearly to normal by a slight increase in the intake of thiamin, although this was still not sufficient to prevent the development of cardiac failure. Two other dogs became moderately paralyzed, and the last two dogs exhibited no evidences of paralysis at any time.

Four other dogs failed to exhibit any evidences of cardiac failure. One of these showed no signs of thiamin deficiency at all, presumably because of coprophagy; one other showed only slight paralysis and was suspected of coprophagy; and two others became very emaciated and paralyzed. In both dogs and pigeons,²² emaciation and severe paralysis definitely delayed or prevented the development of cardiac failure.

In dogs with chronic thiamin deficiency an infusion with 10 per cent glucose in saline was followed in twelve to twenty-four hours by the

appearance of leg weakness (two cases) or cardiac failure (one case). Because of the apparent cause and effect relationship of the injection of glucose and the appearance or exacerbation of symptoms of thiamin deficiency, the use of this infusion fluid was abandoned.

(b) *Pathologic Observations:* Generally similar gross pathologic changes were found in all thiamin-deficient dogs that died from cardiac failure. There was frothy serosanguineous exudate in the trachea and bronchi; the lungs were purple to red in color, especially in dependent parts; and much frothy fluid could be expressed from them. Each pleural cavity contained from a few cubic centimeters to 150 c.c. of bloody fluid. The liver and kidneys were slightly engorged with blood



Fig. 1.—Section from cardiac muscle of a dog that died from cardiac failure. Note the area of necrosis, infiltrated with polymorphonuclear leucocytes, and the normal appearing muscle fibers at the periphery of the lesion (fixed in Zenker's-acetic acid solution and stained by eosin and methylene blue).

in two cases and normal in the others. The left ventricle and auricle were markedly dilated. All of the heart valves were normal grossly. Histologic study revealed some general shrinkage and pale indistinct staining of the muscle fibers in all the hearts. In three cases, small

scattered areas of myocardial necrosis were observed, many of which were infiltrated with polymorphonuclear leucocytes (Fig. 1). Histologic study of the lungs in all cases revealed edema and congestion (Fig. 2).

With the exception of the contracted left ventricle, which was also observed in dogs by Porto and De Soldati,²¹ these abnormalities are compatible with left ventricular failure. The explanation for this apparent discrepancy is not known, but it may be pointed out that rigor mortis develops very soon after death in severely deficient pigeons, and that a



Fig. 2.—Section of lung from the same animal. Note the engorged capillaries and the pink staining edema fluid in the alveoli and bronchiole (fixed in Zenker's acetic acid solution and stained by eosin and methylene blue).

contracted heart is frequently found in pigeons that have died from cardiac failure.²² It is quite possible that this contraction of the heart of the dog and pigeon occurs after death, for recent studies on man by Dr. Gustave Nylin* indicate that this is possible.

*Personal communication. This investigator found that the volume of a greatly enlarged heart could become reduced to half its pre-mortem size a few hours after death. The cardiac volume was computed from roentgenologic studies made before and after death, and the post-mortem volume was confirmed directly at autopsy.

(c) *Physiologic Observations:* Although five dogs died from cardiac failure, and a large number of *infusion tests** were performed on thiamin-deficient dogs that were vomiting or paralyzed, in only three instances were we able to demonstrate that the functional reserve (as measured by the infusion test) was diminished. In three other dogs (two died, and one recovered after thiamin administration) cardiac failure developed so rapidly that detailed studies could not be made, although the animals were observed. This testifies to the difficulty of producing and controlling cardiac failure once it has appeared. However, in one dog (Dog 11) significant circulatory and electrocardiographic observations during cardiac failure were recorded, and these will now be described. Electrocardiograms were recorded on one other dog with dyspnea and pulmonary edema, and they will be mentioned later.

Dog 11 (weight 14.6 kg.) received 350 and, later, 300 Gm. of the experimental diet, plus 225 and, later, 150 micrograms of thiamin by tube daily for twelve weeks. The ration was then reduced to 225 Gm. and the thiamin to 75 micrograms; two days later labored breathing appeared (made worse by the slightest exertion), and pulmonary râles developed. Electrocardiographic studies at this time showed definite elevation of the S-T segment in all leads (Fig. 4, Plate I) and tachycardia (Chart I). Fifteen hundred micrograms of thiamin were given intravenously, and thirty minutes later the dyspnea had disappeared and normal activity was resumed. The deficient diet was continued, and fifteen days later vomiting recurred; thiamin (75 micrograms daily) was then added to the ration again. Two days later, routine morning electrocardiograms revealed once more an elevation of the S-T segment in all leads (Fig. 9, Plate II). As dyspnea at rest was not yet evident, and the general condition of the dog was good, she was anesthetized with chloralose and prepared for an infusion test. The basal cardiac output was found to be 3.71 liters per minute, and an infusion with normal saline at a speed of 57 c.c. per minute was administered (Chart II). Such an infusion had been easily handled by this dog on many previous occasions, and at this time, except for a greater rise in the venous pressure, the response was normal. Ten minutes after the infusion ended, and while the venous pressure was dropping normally, dyspnea appeared, accompanied by pulmonary râles. Blood was drawn immediately from the right side of the heart and femoral artery to ascertain the cardiac output, which was found to be 3.10 liters per minute. Since in normal dogs the cardiac output ten minutes after completion of an infusion was always double or nearly double their basal cardiac output, and since this dog's basal cardiac output on this occasion was 3.71 liters per minute, this was a

*This test has been described in a paper to be published.²³ In carrying out this test, fluid was administered intravenously, in a known volume, and at a constant rate, and its effect estimated by observing the venous pressure, cardiac output, and pulse rate. The changes which occurred in these measurements, during such an infusion, gave an indication of the heart's ability to handle the increased "load," and in so doing gave an estimate of the functional reserve of the myocardium.

Fig. 3.



Fig. 4.

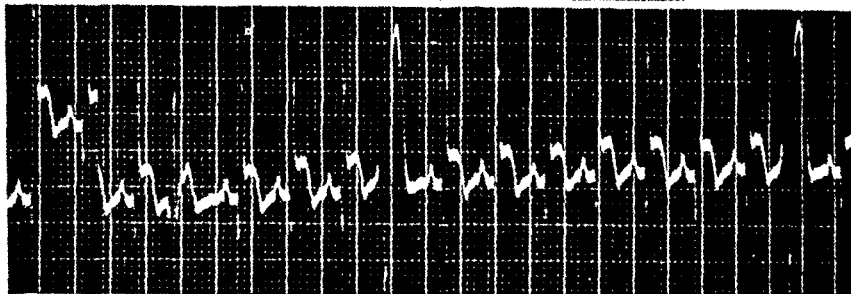


Fig. 5.

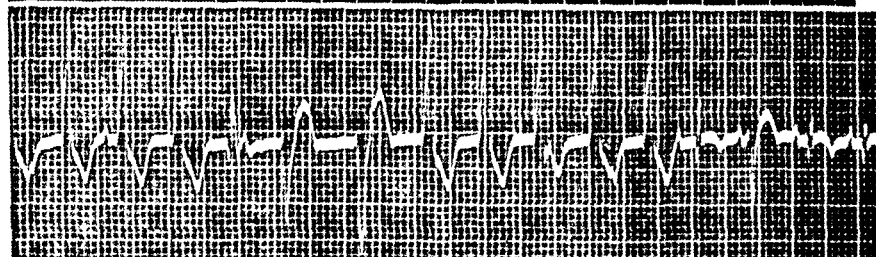


Fig. 6.

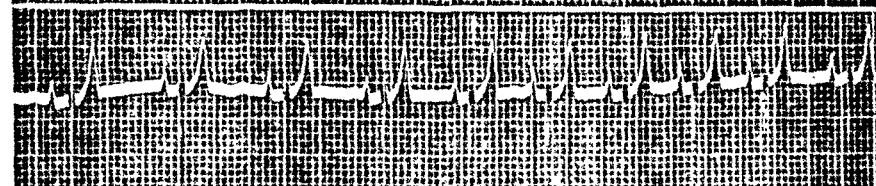


Fig. 7.

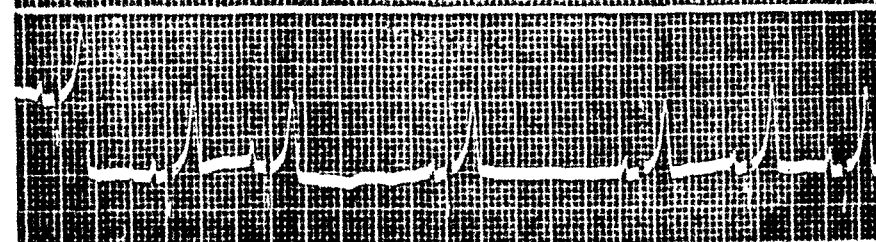


Fig. 8.

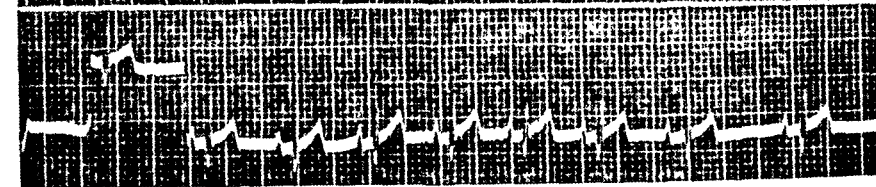


Plate I.—Series of Lead II electrocardiograms from Dog 11 during and between three attacks of cardiac failure. The daily basal heart rate during this period is shown in Chart II.

Fig. 3.—Normal control record taken before Dog 11 was placed on the experimental diet.

Fig. 4.—(June 13.) During first period of failure; note tachycardia (rate 210), marked change in the T waves, and extrasystoles (1,500 micrograms of thiamin were given intravenously immediately after this record was taken).

Fig. 5.—(June 15.) Note runs of ventricular extrasystoles (rate 180).

Fig. 6.—(June 18.) Normal rhythm; note elevated T waves (rate 150).

Fig. 7.—(June 23.) Normal rhythm; note elevated T waves (rate 80).

Fig. 8.—(June 28.) Apparently the cardiac musculature is becoming deficient again; note tachycardia (rate 135) and beginning changes in T waves.

low output. Thiamin (500 micrograms) was given intravenously, and in ninety minutes the dyspnea and pulmonary edema had practically disappeared and the S-T segment of the electrocardiograms had returned nearly to normal (Fig. 13, Plate II). Dog 11 continued to receive the deficient diet and fourteen days later was found dead in her cage. Her post-mortem weight was 14.2 kg., so that she lost only 0.4 kg. while receiving the thiamin-deficient diet.

Chart I shows the daily basal pulse rate of Dog 11 from the first attack of cardiac failure until death. Each period of failure was accompanied by tachycardia, which appeared several days before either dyspnea or abnormalities in the electrocardiograms were noted. When thiamin was given, the cardiac rate decreased gradually to normal during a period of several days. Preceding the onset of cardiac failure by two days,

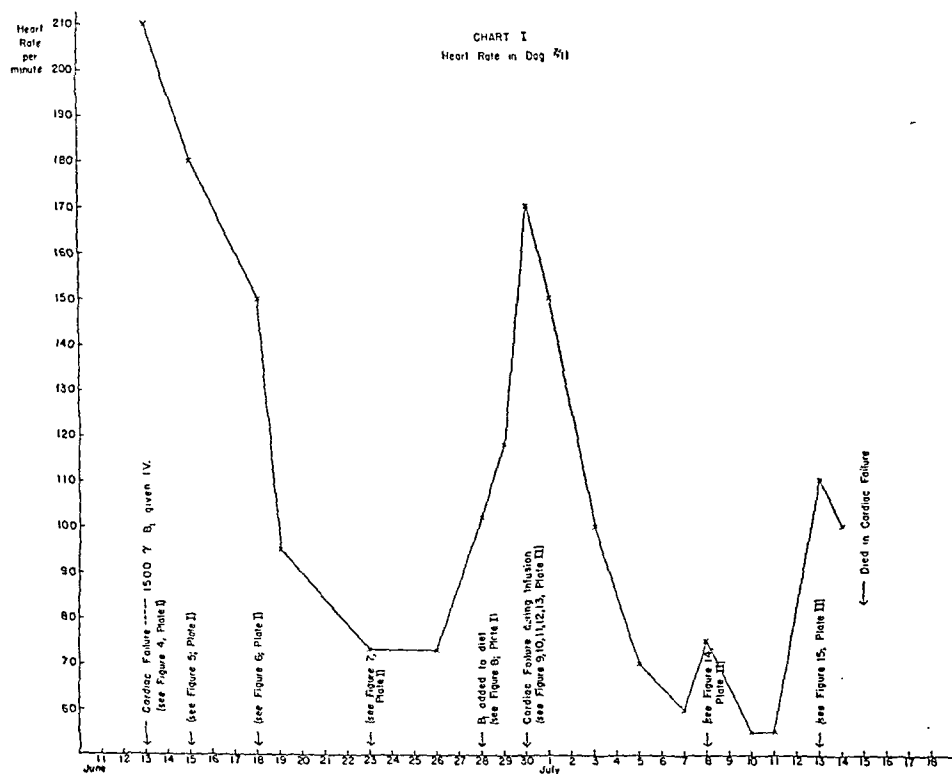


Chart I.—This chart shows the daily basal pulse rate of Dog 11 from the first attack of cardiac failure until her death. These cardiac rates were obtained by auscultation after the dog had rested for thirty minutes and was quiet and calm. The days on which the electrocardiograms in Plates I and II were taken are indicated in the chart.

slight but definite abnormalities were noted in the electrocardiograms (Fig. 8, Plate I; and Fig. 15, Plate II). With the appearance of dyspnea and pulmonary rales these changes became greater (Fig. 4, Plate I; and Fig. 9, Plate II). After thiamin was administered, the electrocardiographic complexes returned nearly to normal in about ninety minutes (Fig. 13, Plate II), but the dominant rhythm was then

Fig. 9.

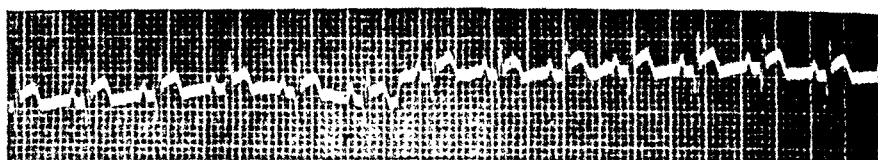


Fig. 10.

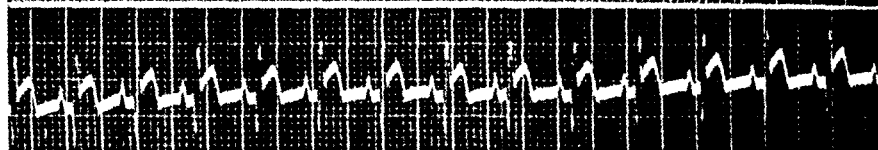


Fig. 11.

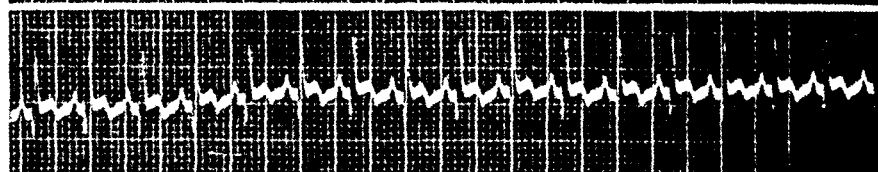


Fig. 12.

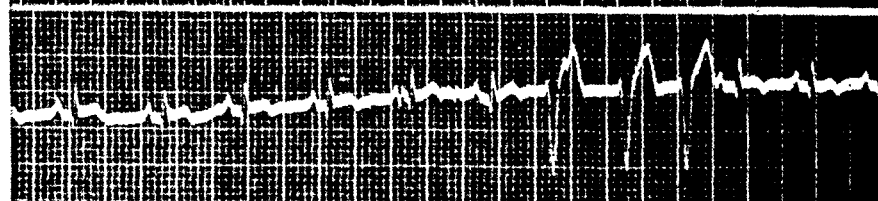


Fig. 13.

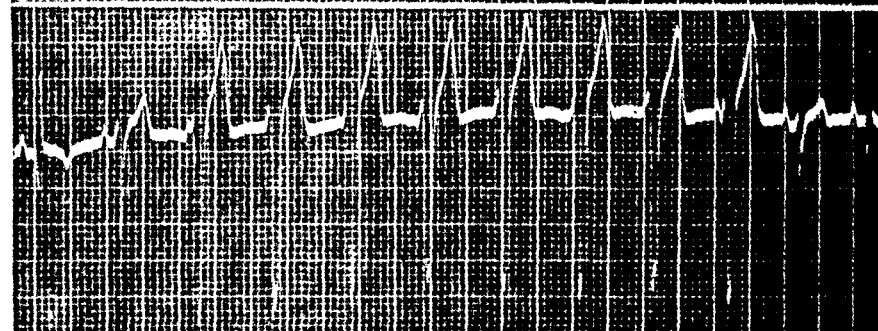


Fig. 14.

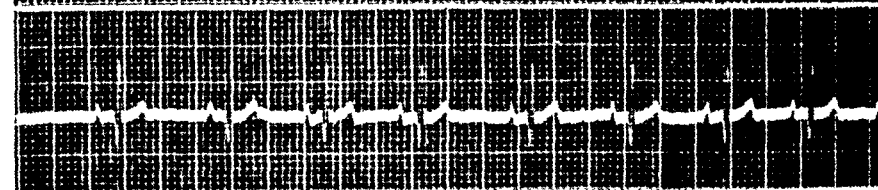


Fig. 15.

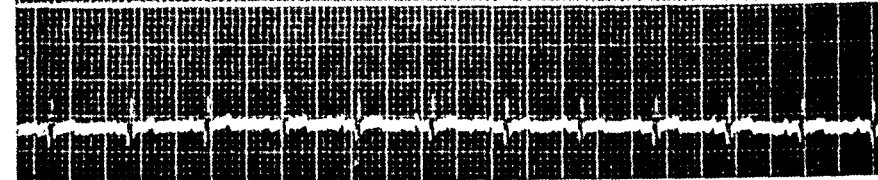


Fig. 9.—(June 30.) Dyspnea on effort present; note increased cardiac rate (165) and elevation of the S-T segment.

Fig. 10.—(June 30; two hours later.) Dyspnea and pulmonary râles present after conclusion of infusion test. Note T waves.

Fig. 11.—(June 30; ten minutes after thiamin was given intravenously.) Note return of T waves toward normal.

Fig. 12.—(June 30; thirty-five minutes later.) Cardiac rate slower (rate 150); note further changes in the T waves and ventricular extrasystoles.

Fig. 13.—(June 30; ninety minutes after thiamin was given.) Note the T waves and frequent ventricular extrasystoles.

Fig. 14.—(July 8.) Normal appearing complexes.

Fig. 15.—(July 13.) Note the very slight abnormalities in the electrocardiograms and tachycardia. Two days later this dog was found dead in her cage from cardiac failure.

disturbed by numerous extrasystoles which were present for three to four days. Later during the period of recovery the T waves became elevated to a height of 1 cm. (Fig. 7, Plate I).

The pathologic changes in Dog 11 are of especial interest. In addition to marked pulmonary edema and congestion, and a right-sided hydrothorax of 150 c.c. and left-sided hydrothorax of 50 c.c., there were some congestion of the liver and kidneys and edema of the posterior abdominal wall. The right auricle and ventricle were dilated, and the left ventricle was normal in size. Grossly, the heart muscle appeared pale, but otherwise normal, and the endocardium and pericardium appeared normal. Histologically, the myocardium revealed two distinct types of lesions. Small areas of focal necrosis (some with inflammatory cell infiltration) were scattered throughout the myocardium; these were similar to those described before, and illustrated in Fig. 1. In addition, there were other

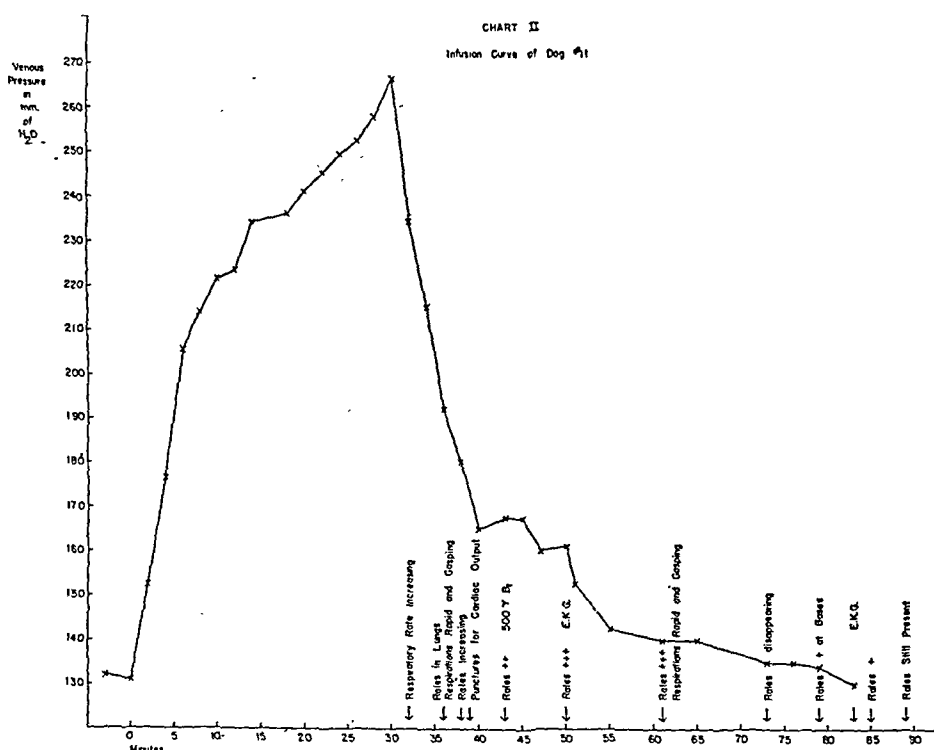


Chart II.—Chart of the infusion curve of Dog 11 on June 30, indicating the time relationship between appearance of rales in the lungs and completion of the infusion. Venous pressure measurements were made with the zero point of the manometer at the skin of the dog's back. The infusion curve rose at a constant rate for exactly thirty minutes, beginning at zero minutes.

focal lesions which appeared to be definitely older. They consisted of small areas of loose connective tissue from which myocardial fibers were obviously absent. These lesions were generalized and were of about the same size as the areas of focal necrosis. Although these focal lesions were seen in every microscopic field, by far the majority of muscle fibers appeared entirely normal.

(d) *Additional Observations:* In one of the other dogs with dyspnea and pulmonary edema (râles), electrocardiographic studies revealed definite, although moderate, changes in the myocardial action potentials. The Q waves in Lead I disappeared and in Lead III became very prominent, and the T waves in Lead I became more prominent and elevated and in Leads II and III inverted. These changes were accompanied by a tachycardia of 110, 135, and 120 (three observations within two hours). General improvement, which appeared to start spontaneously and was hastened by an intravenous injection of thiamin, was accompanied by a marked reduction in the cardiac rate and a very rapid return of the electrocardiogram to normal. In another animal, subcutaneous edema was observed in all extremities without other evidence of circulatory embarrassment or abnormalities in the electrocardiogram. This probably was not cardiac edema, but may have represented some other disorder due to thiamin deficiency.

DISCUSSION

The means by which cardiac failure can be produced in thiamin-deficient pigeons have been outlined and discussed elsewhere.²² The same general principles of dietary management produce a similar state in the dog. When a thiamin-deficient ration is consumed voluntarily by dogs, anorexia and a consequent, marked emaciation usually result.^{20, 24} The animals may consume the deficient diet for two or three months before they develop paralysis, and they rarely (if ever) show evidences of cardiac failure. If the animals are made acutely deficient by tube feeding and small supplements of thiamin, only an insignificant loss of weight occurs (approximately 10 per cent); ataxia of the hind legs appears in about twenty-one days and becomes very severe a few days later if thiamin is not administered in large amounts. In such animals opisthotonus and extensor rigidity may develop. This has also been observed in cats by Odom and McEachern.* In acutely deficient dogs and pigeons, dyspnea, pulmonary râles, and post-mortem evidences of cardiac failure fail to appear, although a few acutely deficient pigeons with opisthotonus have exhibited minor changes in their electrocardiograms.²²

To assure the production of cardiac failure, it is necessary, first, to deplete the animal's reserve of thiamin slowly by feeding it on a diet which is only slightly deficient in thiamin. According to our maintenance requirement studies, the practical thiamin requirement of dogs that consumed our experimental diet was about 60 micrograms (intra-

*Personal communication. These investigators found that tube-fed cats developed paralysis from thiamin deficiency in approximately three weeks. Although considerable weight loss occurred, three of their animals developed convulsive attacks consisting of opisthotonus and extensor rigidity of the extremities, and frequent clonic movements of all extremities. These attacks were quickly alleviated by thiamin.

muscularly) per 100 Gm. of diet,* which figure agrees favorably with that given by Arnold and Elvehjem.²⁵ Thus, if, subsequent to vomiting, 60 micrograms of thiamin, or less (40 micrograms), are given orally with every 100 Gm. of diet, a gradual depletion of the thiamin reserve results. When a dog becomes accustomed to tube feeding, the thiamin can be gradually reduced to 30 or even 20 micrograms per 100 Gm. of diet, but, if vomiting recurs or paralysis develops, the thiamin dosage should be increased. Mild ataxia in both dogs and pigeons frequently improved rapidly, and normal gait was restored when the thiamin dosage was increased slightly, i.e., from 30 to 40 or 50 micrograms per 100 Gm. of diet (dogs), even though the diet was still deficient in thiamin, and cardiac failure developed. In order to be sure of stopping the vomiting or increase of paralysis, it was found expedient, when paralysis appeared, to give one intramuscular injection of 100 or 200 micrograms of thiamin. In addition, the daily oral dosage of thiamin was increased slightly, depending upon the severity and acuteness of the paralysis.

It is important to avoid the development of severe paralysis or of a greater than 10 per cent loss of weight, for either or both tend to prevent the appearance of cardiac failure. Keefer³ observed that, in patients with beriberi, paralysis tended to delay or prevent the onset of heart failure. It is quite likely that these two factors prevented the development of cardiac failure in De Soldati's dogs,²⁰ although tachycardia and abnormal electrocardiograms were noted ante mortem, and evidences of myocardial changes were observed post mortem. Perhaps emaciation and inactivity caused by paralysis reduce the work of the heart sufficiently to compensate for its impaired efficiency.

Several variable factors which may delay or prevent the appearance of thiamin deficiency in the dog are vomiting, coprophagy, and a high and variable thiamin content of yeast. As the thiamin requirement becomes reduced in proportion to the amount of the day's ration which is vomited or not consumed,^{26, 27} it is possible by vomiting to reduce the thiamin requirement below the amount that is being administered intramuscularly. This complication can be minimized by mixing the thiamin with the day's ration. A second cause for failure, coprophagy,^{28, 29} was suspected but never directly observed in one dog that received the experimental diet and no thiamin for six months without becoming deficient, and in another in which the onset of the deficiency was delayed. The thiamin content of different samples of yeast, all of which had been autoclaved in an alkaline medium at a pressure of 20 pounds for six hours, was found to vary significantly. This made it very difficult to know how much thiamin to add to the diet, but the problem was partially solved by reducing the yeast content of the diet from approx-

*This dosage of thiamin protected two chronically depleted dogs from vomiting, paralysis, and heart failure during a period of about eight weeks. It is quite possible that the true requirement is higher than this, because the tissue stores are able to supply some thiamin even though they are already very low. In this event some animals might become thiamin deficient on this dosage, especially if the experimental period were longer. It should be noted that our diet contained slightly more fat than the one used by Arnold and Elvehjem²⁵ in their experiments on dogs.

imately 10 per cent to 5 per cent, and by later utilizing a single source of this substance. On the other hand, glucose infusions, by greatly increasing the thiamin requirement, increased an already existing thiamin deficiency, with the result that paralysis or cardiac failure appeared suddenly.

Our limited observations on thiamin-deficient (but not starved) dogs indicate that the basal pulse rate may increase gradually during a period of four or five days preceding the appearance of definite cardiac failure. This is contrary to the observations of those investigators who believe that experimental thiamin deficiency in rats and pigeons is accompanied by bradycardia,¹¹⁻¹⁶ but in essential agreement with others who consider that this bradycardia is the result, in large part at least, of concomitant starvation.¹⁷⁻¹⁹ It should be noted that tachycardia is almost invariably present in human beings with beriberi heart failure,¹⁻⁵ and that De Soldati²⁰ noted tachycardia in his thiamin-deficient dogs. In our dogs this tachycardia was accompanied (and possibly caused) by a gradually increasing nervousness, irritability, and increased tendency to vomit. Twenty-four to forty-eight hours before dyspnea at rest was evident, changes in the electrocardiogram appeared. These were similar to those described in rats and man by Weiss, et al.,^{4, 5, 12} in man and pigeons by others,^{1-3, 6, 11} and in the dog by De Soldati.²⁰ In one of our cases (Dog 11) the electrocardiographic changes consisted of depression and later a high take-off of the T waves in all leads, and in another dog less dramatic alterations were noted in the Q and T waves in Leads I and III. These changes were accompanied by dyspnea and pulmonary râles in both dogs, and in Dog 11 on a second occasion by a reduction in the cardiac reserve, as demonstrated by the infusion test. An intravenous injection of as little as 100 micrograms of thiamin caused the dyspnea and pulmonary râles to disappear rapidly, the electrocardiogram to approach normal in one to two hours, and the pulse rate to slow gradually to normal over a period of several days.

Electrocardiograms of thiamin-deficient pigeons which were allowed to lose very little or no weight have demonstrated very similar events.²² The cardiac rate increased gradually during a period of several days before and while the electrocardiograms showed abnormalities. When thiamin was given intravenously (or intramuscularly), the electrocardiogram returned to normal in sixty to ninety minutes and the cardiac rate slowed to normal in twenty-four to forty-eight hours. When the food intake was reduced so that a rapid loss of weight occurred, the changes were similar to those observed in the dog.

The lesions observed in the cardiac musculature of these dogs (as also those reported in the pigeon³¹ and man^{4, 5, 7}) do not appear great enough to cause cardiac failure, especially in a few instances in which the areas of necrosis were very difficult to find microscopically. However, the very rapid return to normal of the electrocardiographic complexes after thiamin had been injected indicates that many more muscle fibers in the

heart were impaired functionally, and that these were capable of resuming normal function, as indicated by the electrocardiograms very soon after they were supplied with thiamin. It is possible that less severe myocardial changes, such as those observed by Porto and De Soldati, as well as many completely normal appearing myocardial fibers, were among those that were quickly restored to normal by thiamin. It seems reasonable to suggest, however, that repeated attacks of cardiac failure from thiamin deficiency, accompanied by necrosis of myocardial cells such as was observed in Dog 11, might result finally in a marked reduction of the functioning heart muscle, and its replacement by connective tissue. In such cases chronic cardiac failure might well develop, and probably would not be influenced so dramatically by the administration of thiamin. This is in agreement with a statement of Weiss³⁰ that, under thiamin therapy, the speed of recovery of patients with cardiac failure caused by beriberi is variable, and may require several weeks or longer.

The dyspnea and pulmonary râles ante mortem and pulmonary congestion and edema post mortem indicate that the cardiac failure in our thiamin-deficient dogs was primarily of the left ventricle. Had these animals survived longer (had failure been less acute), it is possible that obvious systemic congestion, with edema, similar to that observed in human beriberi, would have developed. The presence of bilateral hydrothorax, congestion of the liver, and edema of the posterior abdominal wall in Dog 11, and of smaller hydrothoraces with less hepatic congestion in several other dogs, indicated that some degree of right ventricular failure had already appeared.

SUMMARY AND CONCLUSIONS

When dogs were fed a diet partially deficient in thiamin and a significant loss of weight was prevented by tube feeding, they developed dyspnea and pulmonary edema, and, at post-mortem examination, presented pulmonary congestion, edema, and other abnormalities which supported a diagnosis of cardiac failure, chiefly of the left ventricle. Histologic study of their myocardiums revealed many small areas of necrosis. Electrocardiographic studies revealed definite abnormalities in the electrical activity of the myocardium, and tachycardia just preceding and during such periods of cardiac failure. These changes disappeared quickly after the administration of thiamin. In one dog, circulatory studies showed that the cardiac reserve of thiamin-deficient dogs with dyspnea and pulmonary râles may be reduced. A more extensive consideration of circulatory studies in these and other dogs is to be reported elsewhere.²³

REFERENCES

1. Kepler, E. J.: Beriberi From a Diet of Raw Starch, *J. A. M. A.* 85: 409, 1925.
2. Scott, L. C., and Herrmann, G. R.: Beriberi ("Maladie des Jambes") in Louisiana, *J. A. M. A.* 90: 2083, 1928.

3. Keefer, C. S.: The Beriberi Heart, *Arch. Int. Med.* 45: 1, 1930.
4. Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in Vitamin Deficiency States, *Tr. A. Am. Physicians* 51: 341, 1936.
5. Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi), *Ann. Int. Med.* 11: 104, 1937.
6. Inada, R.: Symptoms and Pathological Aspects of the Disturbances of the Circulatory System in Beriberi, *Libman Anniversary*, New York, 1932, International Press, vol. II, p. 577.
7. Aalsmeer, W. C., and Wenckebach, K. F.: Herz und Kreislauf bei der Beriberi-Krankheit, *Wien. Arch. f. inn. Med.* 16: 193, 1929.
8. Goodhart, R., and Jolliffe, N.: The Role of Nutritional Deficiencies in the Production of Cardiovascular Disturbances in the Alcohol Addict, *AM. HEART J.* 15: 569, 1938.
9. McCarrison, R.: The Pathogenesis of Deficiency Disease, *Indian J. M. Research* 7: 279, 1919.
10. Findlay, G. M.: An Experimental Study of Avian Beriberi, *J. Path. & Bact.* 24: 175, 1921.
11. Méhes, J., and Péter, F.: Die Wirkung des Digitoxins auf das Ekg der normalen und der an experimenteller Beriberi erkrankten Tauben, *Arch. f. exper. Path. u. Pharmakol.* 176: 226, 1934.
12. Weiss, S., Haynes, F. W., and Zoll, P. M.: Electrocardiographic Manifestations and the Cardiac Effect of Drugs in Vitamin B₁ Deficiency in Rats, *AM. HEART J.* 15: 206, 1938.
13. Carter, C. W., and Drury, A. N.: Heart Block in Rice-Fed Pigeons, *J. Physiol.* 68: i, 1929.
14. Drury, A. N., Harris, L. J., and Maudsley, C.: Vitamin B Deficiency in the Rat. Bradycardia as a Distinctive Feature, *Biochem. J.* 24: 1632, 1930.
15. Birch, T. W., and Harris, L. J.: Bradycardia in the Vitamin B₁-Deficient Rat and Its Rise in Vitamin B Determinations, *Biochem. J.* 28: 602, 1934.
16. Baker, A. Z., and Wright, M. D.: A Survey of the Rat-Bradycardia Method of Estimating Vitamin B₁, *Biochem. J.* 33: 1370, 1939.
17. Parade, G. W.: Vitamin B-Untersuchungen; zur Frage des Zusammenhanges zwischen Vitamin B₁-Mangel und Bradykardie, *Ztschr. f. Vitaminforsch.* 6: 327, 1937.
18. Parade, G. W.: Vitamin B-Untersuchungen; Vitamin B₁-Mangel, Bradykardie und Temperatursturz, *Ztschr. f. Vitaminforsch.* 7: 35, 1938.
19. MacDonald, D. G. H., and McHenry, E. W.: Studies on Rat Bradycardia, *Am. J. Physiol.* 128: 608, 1940.
20. De Soldati, L.: Los trastornos circulatorios del perro en avitaminosis B₁. I: El pulso, la tensión arterial y el electrocardiograma, *Rev. Soc. argent. de biol.* 15: 142, 1939.
21. Porto, J., and De Soldati, L.: Alteraciones microscópicas del corazón del perro en avitaminosis B₁, *Rev. Soc. argent. de biol.* 15: 303, 1939.
22. Swank, R. L., and Bessey, O. A.: The Production and Study of Cardiac Failure in Thiamin Deficient Pigeons, *J. Clin. Investigation*, Abstract, 1940.
23. Observations on Certain Manifestations of Circulatory Congestion Produced in Dogs by Rapid Infusion. (Unpublished observations from this laboratory.)
24. Cowgill, G. R.: The Vitamin B₁ Requirement of Man, New Haven, 1934, Yale University Press.
25. Arnold, A., and Elvehjem, C. A.: Influence of the Composition of the Diet on the Thiamin Requirement of Dogs, *Am. J. Physiol.* 126: 289, 1939.
26. Swank, R. L., and Bessey, O. A.: Avian Thiamin Deficiency. Characteristic Symptoms and Their Production. (To be published.)
27. Williams, R. R., and Spies, T. D.: Vitamin B₁ (Thiamin) and Its Use in Medicine, New York, 1938, The Macmillan Co.
28. Bliss, S.: Refection in the Rat, *J. Nutrition* 11: 1, 1936.
29. Salaam, A. A., and Leong, P. C.: Synthesis of Vitamin B₁ by Intestinal Bacteria of the Rat, *Biochem. J.* 32: 958, 1938.
30. Weiss, S.: The Application of Electrocardiography in the Detection of Avitaminosis B₁, *Proc. Round Table on Nutrition and Public Health*, 16th Ann. Conf. Milbank Memorial Fund, March 29-31, 1938, p. 82.
31. Swank, R. L.: Avian Thiamin Deficiency. A Correlation of the Pathology and Clinical Behavior, *J. Exper. Med.* 71: 683, 1940.

CHANGES IN THE RHYTHM OF THE HEART DURING
RESECTION OF THE PERICARDIUM IN CHRONIC
CONSTRUCTIVE PERICARDITIS, AS RECORDED
ELECTROCARDIOGRAPHICALLY

HAROLD J. STEWART, M.D., AND ROBERT L. BAILEY, JR., M.D.
NEW YORK, N. Y.

THAT resection of the pericardium in cases of chronic constrictive pericarditis may be safely performed has been demonstrated by Schmieden, et al.,^{1, 2} Churchill,³ Beck and Griswold,⁴ Heuer, et al.,^{5, 6, 7} and by Blalock, et al.^{8, 9, 10} Heuer and Stewart⁵ have recently reviewed the published data relating to the surgical treatment of this disease, and Stewart and Heuer^{6, 7} and Burwell and Blalock¹¹ have studied the dynamics of the circulation in the presence of this lesion. It is of practical importance to know how the heart behaves during the resection of the closely attached pericardium.

Feil and Rossman¹² have reported the electrocardiographic changes during operation in twenty-four patients who were the subjects of cardiac anastomosis for the treatment of angina pectoris and coronary sclerosis, and in cases in which the pericardium was resected. Patients who were subjected to cardiac anastomosis showed electrocardiographic changes more frequently than those whose pericardiums were resected. Most of the abnormalities occurred during manipulation of the heart. The use of quinidine sulfate preoperatively in certain of the cases appeared to prevent the occurrence of arrhythmias. This impression could not be demonstrated conclusively by comparing the electrocardiograms of these patients with those of subjects who had not received quinidine. Mautz¹³ and Beck and Mautz¹⁴ applied local anesthetics to the surface of the heart in an attempt to reduce its surface irritability during cardiac surgical procedures. They found that applying a solution of procaine directly to the auricles and ventricles reduced the incidence of arrhythmias during operations on the heart in man. This measure was efficacious experimentally in dogs in converting auricular fibrillation to normal sinus rhythm, and also terminated ventricular fibrillation.

Feil and Rossman's¹² observations are the only records in the literature relating to changes in the cardiac rhythm during pericardial resection. We have had the occasion to make electrocardiograms during resection of the pericardium in the last six cases of chronic constrictive pericarditis in which we have used this method of treatment. We had gained the impression from observing the hearts of the other seven patients during operation that disturbances of rhythm were infrequent

From the New York Hospital and Department of Medicine, Cornell University Medical College, New York, N. Y.

Received for publication Oct. 11, 1940.

and of short duration. We wished, however, to ascertain with certainty the nature of the irregularities. These observations are now being reported. In five cases, J. P., C. G., G. S., E. B., and J. C., the operations were performed by Dr. George J. Heuer, as previously described,⁵ and, in the other case, P. M., by Dr. W. D. Andrus. All patients had had the usual preoperative study and treatment.^{5, 6, 7} The three standard leads of the electrocardiogram were taken after the patient had been placed on the operating table. This served as a control. Another electrocardiogram was taken after anesthesia had been induced by the use of open drop ether, and subsequent ones at frequent intervals throughout the operative procedure, namely, when the chest was opened, when dissection of the pericardium was started, and at frequent intervals during resection. A final record was made after the chest had been closed. From seven to twelve electrocardiograms were taken during each operation.

OBSERVATIONS

J. P., History No. 155618, a man, aged 36 years, was admitted to hospital Nov. 4, 1938. He had suffered from dyspnea on exertion, swelling of the legs and abdomen, and palpitation, for eight years. There was no history of rheumatic fever, tuberculosis, or any other illness which might have been the etiologic factor in the production of chronic constrictive pericarditis. He presented the following signs and symptoms: dyspnea, cyanosis, massive edema of the legs, marked distention of the superficial veins, fluid in the right pleural cavity, marked enlargement of the liver, and marked ascites. The heart did not appear to be enlarged; there were no abnormal signs on auscultation. Auricular fibrillation prevailed. The blood pressure measured 108/68. The radial pulse was paradoxical. The venous pressure was elevated to 305 mm. of saline, and the arm-to-tongue circulation time (Decholin) was prolonged to 26.4 seconds. Roentgenograms of the heart did not show calcification of the pericardium; fluoroscopic examination of the heart showed diminished amplitude of the cardiac pulsations. On Feb. 14, 1939, when the signs and symptoms had been alleviated by medical treatment,⁶ resection of the pericardium was performed. The pericardium was found to be markedly thickened, and the parietal pericardium was everywhere adherent to the surface of the heart. Calcification of the pericardium was not observed. Resection of the pericardium over the entire anterior surface of both ventricles and the apex of the heart was carried out by careful sharp and blunt dissection.

The preoperative electrocardiogram showed auricular fibrillation, with a ventricular rate of 90 per minute. The QRS complexes were low and slightly split. The T waves were diphasic in all leads. The patient had been well digitalized to keep the ventricular rate slow,^{5, 6, 7} and the form of the T waves was in part a digitalis effect. The QRS conduction time was within normal limits, and there was no deviation of the electrical axis. An increase in the ventricular rate from 90 to 120 per minute was the only change in the electrocardiogram until pericardial resection was begun. At this time, ventricular premature contractions occurred. Both left and right ventricular premature contractions,* but more of the former, appeared while the pericardium covering the anterior surface of the left ventricle was being resected. Shortly after the resection of the pericardium from the anterior surface of the left ventricle had been started, there were two left ventricular premature contractions in succession; after this there were four left ventricular premature contractions in succession, forming a short run of ventricular parox-

*Old terminology.

ysmal tachycardia. When resection of the pericardium from the left ventricle had been partially completed, several right ventricular premature contractions were recorded. These occurred singly and in pairs, and appeared to arise from different foci. As resection over left ventricle neared completion, occasional left ventricular premature contractions occurred singly, and there was a series of five left ventricular contractions in succession, constituting a short run of ventricular paroxysmal tachycardia. A single right ventricular premature contraction appeared while the right ventricle was being uncovered, and a left ventricular premature contraction was recorded after resection had been completed. On comparing the records taken before and at the completion of the operation, the T waves in Lead I had increased slightly, and the QRS complexes in Lead II were decreased slightly, in amplitude. On the whole, however, the series of electrocardiograms showed no changes of significance except the ventricular premature contractions and the short runs of ventricular paroxysmal tachycardia.

C. G., History No. 97484, a white man, aged 33 years, was admitted to hospital May 20, 1939. He stated that he had suffered from dyspnea on exertion for twelve years and from a feeling of fullness in the epigastrium after exertion for seven years. He had never had orthopnea, edema, ascites, or precordial pain. There was no history of rheumatic fever, tuberculosis, or any other infection which might have been the etiologic factor in the production of chronic constrictive pericarditis. The patient presented the following signs and symptoms: cyanosis, distention of the superficial veins, fluid in the right pleural cavity, and enlargement of the liver. The heart did not appear to be enlarged, and no murmurs were heard. The rhythm was normal. The blood pressure measured 130/90. The radial pulse was paradoxical. A roentgenogram of the heart showed calcification of the pericardium. Fluoroscopic examination of the heart revealed diminished amplitude of the cardiac pulsations. The venous pressure was elevated to 123 mm. of H_2O , and the arm-to-tongue circulation time (Decholin) increased to 36.4 seconds. Resection of the pericardium was performed May 29, 1939. At operation, calcification of the pericardium was observed along both the right and left borders of the heart. The pericardium over the anterior surface of the heart was not calcified, but the parietal pericardium was adherent to the anterior surface of the heart. Resection of the pericardium over the anterior surface of the heart was carried out by blunt dissection.

The preoperative electrocardiogram showed normal sinus rhythm, with a heart rate of 110 per minute (Fig. 1). The P-R and QRS conduction times were within normal limits. There was slight deviation of the electrical axis to the right. The QRS complexes were slightly split in Leads I and II, and were low and split in Lead III. The T waves were positive in Leads I and II and diphasic in Lead III. The RS-T segments were slightly depressed in Leads II and III. Auricular premature contractions were present in all leads. During operation the heart rate increased, and varied between 120 and 160 per minute. The electrocardiogram which was taken during resection of the ribs showed a paroxysm of auricular fibrillation in Lead I, and, in Lead II, a run of auricular fibrillation, followed by two auricular premature contractions and then a run of auricular paroxysmal tachycardia. As the pleura was being opened, the transition from normal rhythm to auricular fibrillation was recorded in Lead I; Lead II showed auricular fibrillation, which was replaced by one auricular premature contraction and then auricular flutter, with a varying rate of ventricular response. A paroxysm of auricular fibrillation, followed by multiple auricular premature contractions, was recorded as resection of the pericardium from the left ventricle was begun. The record which was taken as the pericardium was being dissected from the right ventricle showed auricular fibrillation, followed by multiple auricular premature contractions and then normal rhythm in Lead I and auricular fibrillation in Lead II. A paroxysm of auricular fibrillation, followed by multiple auricular premature contractions, was recorded

as the pleura was being closed. The final record, taken as the muscle flaps were being closed, showed auricular fibrillation, followed by multiple auricular premature contractions and then another paroxysm of auricular fibrillation. Normal rhythm recurred later in the day and persisted. No ventricular premature contractions were recorded. The slight deviation of the electrical axis to the right disappeared after resection of the pericardium had been completed. The QRS complex in Lead I decreased in amplitude. The T waves varied in amplitude during the procedure, especially in Lead III, in which they changed from diphasic to negative, and finally to positive as the pericardium was being resected. The T waves in Lead I decreased slightly in amplitude, and, in Lead II, increased slightly in amplitude. In this case the changes which were recorded were an increase in the frequency of the auricular premature contractions and paroxysms of auricular fibrillation, auricular flutter, and auricular paroxysmal tachycardia.

G. S., History No. 232001, a white man, aged 52 years, was admitted to hospital May 25, 1939. At the age of 15 years he suffered from cough for six months, and during this period an opening in the skin over the suprasternal notch appeared, from which pus drained. At the age of 34 years he suffered from "double pneumonia," and was told at this time that his heart was enlarged and "irregular." He experienced no cardiac symptoms until he was 45 years of age, seven years before admission, when he began to suffer from swelling of the abdomen, which progressed steadily in severity. He had never had dyspnea, orthopnea, or edema. The patient presented the following signs and symptoms: slight cyanosis, marked distention of the superficial veins, fluid in both pleural cavities, enlargement of the liver, and marked ascites. The heart did not appear to be enlarged, and no murmurs were heard. Auricular fibrillation was present. The blood pressure

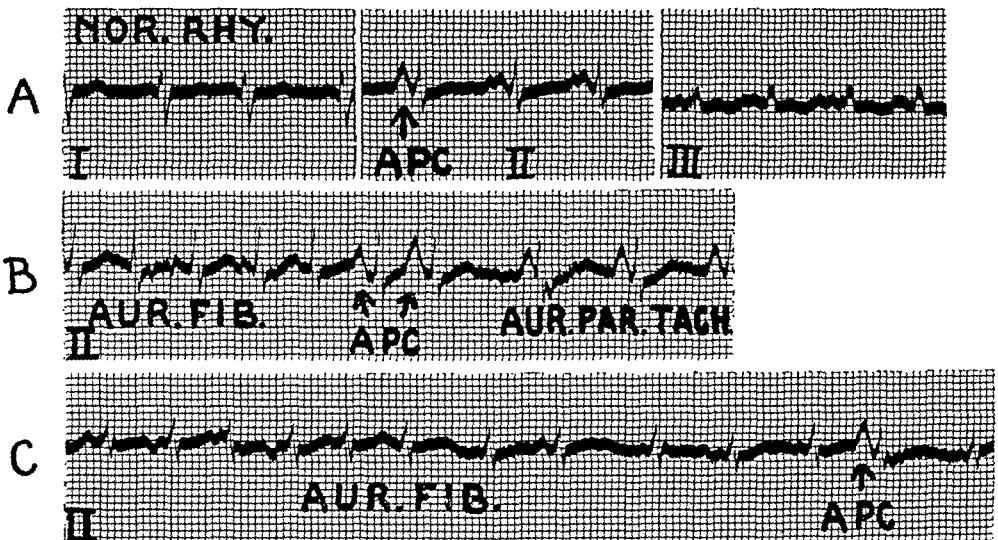


Fig. 1.—Electrocardiograms of C. G. A was taken before anesthesia was induced; normal rhythm (*Nor. Rhy.*) prevailed, and one auricular premature contraction (*APC*) was recorded in Lead II. B was taken during resection of the ribs, and shows paroxysmal auricular fibrillation (*Aur. Fib.*), followed by two auricular premature contractions (*APC*) and then a run of auricular paroxysmal tachycardia (*Aur. Par. Tachy.*), apparently from the same focus as the auricular premature contraction in Lead II, in A. C was taken after closure of the chest, as the muscle flaps were being sutured. There were recurrence of auricular fibrillation (*Aur. Fib.*) and one auricular premature contraction (*APC*). In this figure, as well as in Fig. 2, divisions of the ordinates equal 10-4 volts, and divisions of the abscissae equal 0.04 second. The electrocardiograms are reduced to three-quarters of their original size. The leads which are reproduced are indicated.

measured 112/74. The radial pulse was paradoxical. The venous pressure was 173 mm. of saline, and the arm-to-tongue circulation time was increased to 23.9 seconds (Decholin). Roentgenograms of the heart showed calcification of the pericardium. Fluoroscopic examination of the heart revealed diminished amplitude of the cardiac

pulsations. After suitable preoperative treatment, the thickened and partially calcified pericardium was resected from the anterior surface of the left and right ventricles.

The preoperative electrocardiogram showed auricular fibrillation, with a ventricular rate of 107 per minute and slight deviation of the electrical axis to the right (Fig. 2). The QRS conduction time was within normal limits. The QRS complexes in Lead I were split and small, in Leads II and III, slightly split. The T waves were positive in Lead I, diphasic in Lead II, and negative in Lead III, and the RS-T segments were slightly depressed in Leads II and III. The patient was receiving digitalis to keep the ventricular rate slow. Auricular fibrillation persisted during the operation, with a ventricular rate which varied between 80 and 100 per minute. The slight deviation of the electrical axis to the right disappeared after the ribs had been resected, but reappeared after the chest was closed. There was no appreciable change in the QRS complexes except for a slight decrease in their amplitude in Leads II and III after the pericardium had been opened. The T waves changed in form and amplitude during the procedure. The T wave in Lead I became negative after resection of the ribs, became more negative during resection of the pericardium, and then became less negative after the wound was closed. The T wave in Lead II showed little change. The T wave in Lead III became diphasic after the ribs had been resected and showed small variations in amplitude during the progress of the operation. A single ventricular premature contraction was recorded in Lead II as the pleura was being resected. As the pericardium was being resected from the right ventricle, a single ventricular premature contraction was recorded in Lead II; four right ventricular premature contractions in succession in Lead III formed a short run of ventricular paroxysmal tachycardia, followed by a single left ventricular premature contraction and then a single right ventricular premature contraction. A single right ventricular premature contraction was recorded as resection of the pericardium was completed.

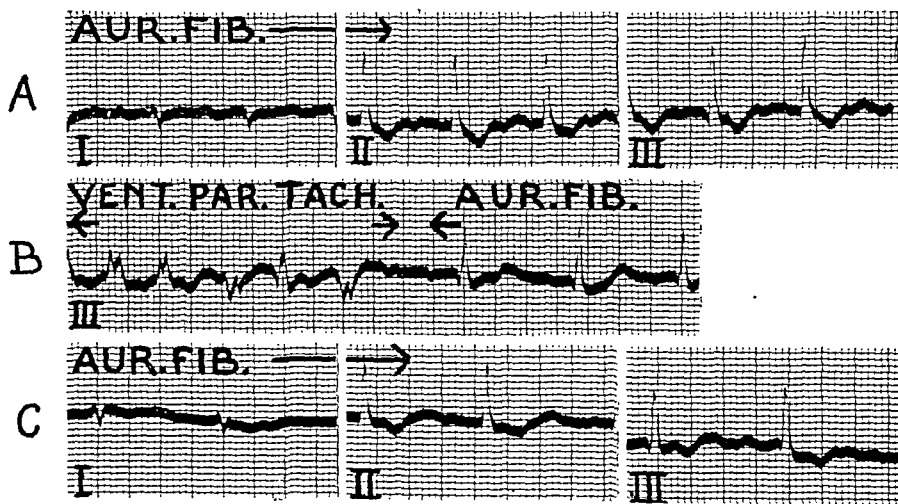


Fig. 2.—Electrocardiograms of G. S. A was taken before induction of anesthesia. Auricular fibrillation (*Aur. Fib.*) was present. B, taken during resection of the pericardium from the right ventricle, shows a run of ventricular paroxysmal tachycardia (*Vent. Par. Tachy.*), with reversion to auricular fibrillation (*Aur. Fib.*). C, taken after completion of the operation, shows persistence of auricular fibrillation (*Aur. Fib.*)

E. B., History No. 233623, a white man, aged 22 years, was admitted to hospital Sept. 19, 1939. Two years before, he had experienced weakness and dizziness on sudden exertion. Swelling of the abdomen and frequent attacks of vomiting soon appeared. About one and one-half years before admission, he began to suffer from

dyspnea on exertion, edema of the feet and legs, varicose veins of the legs, and cyanosis of lips, finger tips, and ears.

Examination showed cyanosis of the lips and nail beds, fluid in the left pleural cavity, distention of the superficial veins, enlargement of the liver (10 cm. below the right costal margin) and spleen (1 cm. below the left costal margin), edema of the legs and scrotum, and varicose veins of the legs. The heart was not enlarged, the rhythm was normal, the apex impulse was neither seen nor felt, the blood pressure was 114/88, and the pulse was paradoxical. The venous pressure was elevated to 186 mm. of saline, and the arm-to-tongue circulation time was prolonged to 25.0 seconds (Decholin). Roentgenographic and fluoroscopic examination did not reveal calcium in the pericardium; the cardiac pulsations were decreased. After suitable preoperative treatment, the thickened pericardium was resected from the anterior surface of the left and right ventricles.

The preoperative electrocardiogram showed normal sinus rhythm, with a rate of 100 per minute. The QRS complexes in Lead I were low and slightly split, the T waves were diphasic in Leads I and II and negative in Lead III, and the R-T segments were slightly depressed in all leads. The heart rate increased after the induction of anesthesia to 111 beats per minute, and tachycardia persisted throughout the procedure; the rate returned to 100 beats per minute after the chest had been closed. There were slight changes in the amplitude and contour of the T waves and slight variations in the R-T segments during the operation. After the induction of anesthesia, T₁ became positive instead of diphasic, and T₂ became slightly less negative. T₃ became diphasic after resection of the ribs. T₂ increased slightly in amplitude, and T₃ became less negative after resection of the pleura. After resection of the pericardium from the anterior surface of the right ventricle, T₁ again became diphasic and the R-T segment of Lead III rose to the isoelectric line. The R-T segment in Lead I returned to the isoelectric line, and the R-T segment of Lead III again became depressed after completion of the resection of the pericardium. After the chest was closed, T₂ and T₃ became slightly more negative. A comparison of the records taken before and after operation showed very little change. This patient had neither premature contractions nor other arrhythmias.

P. M., History No. 273718, a white man, aged 42 years, was admitted to hospital Aug. 8, 1940. He had suffered from swelling of the legs and abdomen, and dyspnea on exertion, intermittently for twelve years, and constantly during the two years before admission. He had had numerous respiratory infections. Two years before the onset of symptoms, he had a five months' illness which was diagnosed as "influenza." Swelling of the legs had been present during this illness. There was no history of rheumatic fever or chorea, or of exposure to tuberculosis. He presented the following signs and symptoms: dyspnea, venous engorgement, cyanosis, marked edema of the legs and abdominal wall, fluid in both pleural cavities, enlargement of the liver, and ascites. The heart did not appear to be enlarged on physical examination, and there was no abnormality of the heart sounds. Auricular fibrillation prevailed. The blood pressure measured 104/68. The radial pulse was paradoxical. The venous pressure was elevated to 160 mm. of saline, and the arm-to-tongue circulation time (Decholin) was prolonged to 19.5 sec. Roentgenograms of the heart showed calcification of the pericardium over the anterior surface of the heart. Fluoroscopic and kymographic examination revealed greatly diminished pulsations along the right border of the cardiac shadow. On Sept. 15, 1940, after he had been rendered free of fluid accumulations by medical treatment,⁶ resection of the pericardium was performed. At operation the pericardium was found to be markedly thickened and partially calcified, and the parietal pericardium was adherent to the surface of the heart. Resection of the pericardium over the anterior surface of the heart was carried out by careful sharp and blunt dissection.

The preoperative electrocardiogram showed auricular fibrillation, with a ventricular rate of 110 per minute. The QRS conduction time was within normal limits. The QRS complexes were split, low, and varied in amplitude in Leads I, II, and III. The T waves were negative in Leads I, II, and III, and the R-T segments were slightly depressed in Leads I and II; these abnormalities were probably caused by the digitalis which the patient received to keep the ventricular rate slow. The ventricular rate increased after resection of the ribs, and tachycardia persisted throughout the procedure. There was no change in rhythm, electrical axis deviation, or in the form of the QRS complexes. The T waves in Lead II became diphasic instead of negative after resection of the pericardium over the left side of the heart had been completed, and then became negative again after resection over the right side of the heart had been completed. This patient showed no premature contractions at any time. A comparison of the records taken before and at the completion of operation showed no appreciable change in the form of the electrocardiogram.

J. C.,* History No. 290121, a white boy, aged 7 years, was admitted to hospital March 1, 1940. He had been in good health without symptoms until three months before admission, when he suffered from a respiratory infection associated with cough. He gained weight rapidly, became short of breath on exertion, and the abdomen increased in size. Three weeks after the onset he was admitted to a hospital, where abdominal paracentesis yielded one pint of fluid. He improved on a regimen of rest in bed and digitalis. He was discharged against advice after 48 days in the hospital. At home the fluid intake and activity were restricted, but the abdomen increased progressively in size and he continued to be short of breath. On admission to New York Hospital, the following signs were observed: slight cyanosis of the lips, enlarged tonsils, engorgement of the neck veins, flaring of the ribs, moderate enlargement of the heart to left and right, normal sinus rhythm (rate 108 per minute), a loud systolic murmur over the precordium, best heard in the third left intercostal space near the sternum, signs of free fluid in the left pleural cavity, signs of fluid in the peritoneal cavity, and enlargement of the liver (the edge extended three fingerbreadths below the right costal margin and was not tender). The blood pressure measured 86/65. The radial pulse was paradoxical. The arm-to-tongue circulation time (Decholin) was increased to twenty-one seconds, and the venous pressure measured 207 mm. of saline. On fluoroscopic and roentgenkymographic examination of the heart, pulsations were decreased except in the pulmonary conus region. After a suitable period of preoperative care, a thickened and partially calcified pericardium was resected from the anterior surface of the left and right ventricles.

The preoperative electrocardiogram showed normal sinus rhythm and sinus tachycardia, with a ventricular rate of 167 per minute. The P-R and QRS conduction times were within normal limits, there was no abnormal axis deviation, the QRS complexes were split and low in all leads, T_1 , T_2 were diphasic, and T_3 was negative. During operation the heart rate became somewhat slower; it varied between 140 and 150 per minute, but normal sinus rhythm persisted. The amplitude of the QRS complexes in Leads I and II varied slightly, but showed no appreciable change in form. This patient exhibited neither premature contractions nor other arrhythmias, nor was there any significant change in the form of the T waves and R-T segments during resection of the pericardium.

DISCUSSION

The electrocardiograms in these six cases (Table I) showed premature contractions and paroxysms of abnormal rhythms as the most striking changes during pericardiectomy. Two patients who had auricular fibril-

*We wish to thank Dr. Elvira Ostlund for referring this patient to us.

TABLE I
CHANGES IN THE ELECTROCARDIOGRAMS DURING PERICARDIECTOMY

CASE	RHYTHM PREVAILING BEFORE OPERATION	CHANGES IN RHYTHM DURING OPERATION	CHANGES IN ELECTRICAL AXIS DEVIATION	CHANGES IN T WAVES	CHANGES IN R-T SEGMENTS	CHANGES IN RATE
J. P. male 36 yr.	Auricular fibrillation	Vent. premature contractions; vent. paroxysmal tachycardia	none	T ₁ increased slightly in amplitude	No significant change	Increased from 90 to 125
C. G. male 33 yr.	Normal sinus rhythm with auricular premature contractions	Auric. premature contractions; auric. paroxysmal tachycardia; auric. fibrillation and paroxysmal auric. flutter	Slight rt. axis deviation disappeared	T _{1,2} varied slightly in amplitude; T ₃ became positive instead of diphasic	No significant change	Increased from 110 to 160
G. S. male 52 yr.	Auricular fibrillation	Vent. premature contractions; vent. paroxysmal tachycardia	Slight rt. axis deviation disappeared and reappeared later at completion of the operation	T ₁ became negative instead of positive; T ₃ became diphasic instead of negative	No significant change	Decreased from 107 to 80.
E. B. male 22 yr.	Normal sinus rhythm	none	none	T ₁ changed from diphasic to positive and back to diphasic; T ₃ changed from negative to diphasic	Increased slightly	Increased from 100 to 111
P. M. male 42 yr.	Auricular fibrillation	none	none	T ₂ changed from negative to negative	none	Increased from 110 to 130
J. C. male 7 yr.	Normal sinus rhythm	none	none	none	none	Decreased from 167 to 140

lation showed ventricular premature contractions and short runs of ventricular paroxysmal tachycardia (J. P. and G. S.), and one patient with normal sinus rhythm showed auricular premature contractions, auricular paroxysmal tachycardia, and paroxysms of auricular fibrillation and auricular flutter (C. G.). In two cases of normal sinus rhythm there were neither premature contractions nor other arrhythmias (E. B. and J. C.), and in one case (P. M.) of auricular fibrillation neither premature contractions nor other changes in rhythm occurred. In three cases (G. S., E. B., and P. M.), the T waves changed moderately in form and amplitude during the operation, and in cases E. B. and P. M. the T waves returned to their preoperative form after closure of the wound. In none of the cases were there significant changes in the R-T segments. The absence of more marked changes in the T waves and R-T segments appeared to indicate that, during resection of the thickened and adherent pericardium, there was only slight damage to the myocardium, even though this involved dissecting the visceral pericardium from the heart muscle. The changes which appeared were transient. The arrhythmias which were recorded were premature contractions, singly and in groups, and short paroxysms of ventricular tachycardia, auricular paroxysmal tachycardia, auricular fibrillation, and auricular flutter. These arrhythmias were of short duration and did not recur in the postoperative period. The signs of congestion that were present before operation showed no marked increase, and circulatory failure did not develop following operation. In the two cases of auricular fibrillation, the paroxysmal rhythms were ventricular in origin. On the other hand, in the one case of normal sinus rhythm, the paroxysmal rhythms were auricular in origin; namely, auricular fibrillation, auricular flutter, and auricular paroxysmal tachycardia.

The changes in the electrocardiograms of these six patients were similar, in part, to those reported by Feil and Rossman¹² in a series of eight cases of chronic constrictive pericarditis. However, the paroxysms of auricular tachycardia, auricular fibrillation, and auricular flutter which occurred in case C. G. did not appear in their series, and the transient ventricular fibrillation, nodal rhythm, and shifting pacemaker which they observed did not occur in our cases. They also recorded changes in the S-T segments in three of their cases which did not occur to any significant degree in our series.

The abnormalities in rhythm which we recorded during resection of the pericardium disappeared promptly with cessation of manipulation, or of traction, or of dissection, of the heart. Judging from observation of the hearts during operation, and because of the brief duration of the irregularities, we did not think it necessary to give quinidine to any of the 13 patients¹⁵ who were subjected to pericardiectomy. As experience increased it did not appear to be indicated as a routine procedure. In one of our 13 cases (not one of the six now being reported), arrhythmia

occurred frequently during one stage of the resection. The use of procaine locally did not appear to decrease the irritability of the muscle. Serial electrocardiograms which were taken for months after operation showed surprisingly few changes in the form of the T waves and R-T segments.

SUMMARY

1. Electrocardiograms which were taken before, and at intervals during, resection of the pericardium in six cases of chronic constrictive pericarditis have been described.

2. Two patients who had auricular fibrillation developed both right and left ventricular premature contractions and short runs of ventricular paroxysmal tachycardia. In one case of normal sinus rhythm, auricular premature contractions which had been present beforehand increased in frequency. Moreover, paroxysms of auricular fibrillation, auricular flutter, and auricular paroxysmal tachycardia were recorded. Two patients with normal sinus rhythm and one with auricular fibrillation developed neither premature contractions nor other changes in rhythm. In only one case did the electrocardiograms which were taken before and after operation show appreciable changes in the amplitude and form of the T waves.

3. These observations demonstrate the remarkable amount of manipulation and mechanical stimulation of its surface that the heart can tolerate without the occurrence of prolonged abnormalities of rhythm and without embarrassment of its function. These observations should give assurance to surgeons who undertake the surgical treatment of chronic constrictive pericarditis.

REFERENCES

1. Schmieden and Fischer: Zur Frage der schwierigen Perikarditis, *Schweiz. med. Wehnschr.* 56: 489, 1926.
2. Schmieden and Westerman: Operative Management of Chronic Constrictive Pericarditis, *Surgery* 2: 350, 1937.
3. Churchill, E. D.: Pericardial Resection in Chronic Constrictive Pericarditis, *Ann. Surg.* 104: 516, 1935.
4. Beck, C. S., and Griswold, R. A.: Pericardiectomy in Treatment of Pick's Syndrome, *Arch. Surg.* 21: 1064, 1930.
5. Heuer, G. J., and Stewart, H. J.: The Surgical Treatment of Chronic Constrictive Pericarditis, *Surg., Gynec., and Obst.* 68: 979, 1939.
6. Stewart, H. J., Heuer, G. J., Deitrick, J. E., Crane, N. F., Watson, R. F., and Wheeler, C. H.: Measurements of the Circulation in Constrictive Pericarditis Before and After Resection of the Pericardium, *J. Clin. Investigation* 17: 581, 1938.
7. Stewart, H. J., and Heuer, G. J.: Chronic Constrictive Pericarditis. Dynamics of the Circulation and Results of Surgical Treatment, *Arch. Int. Med.* 63: 504, 1939.
8. Blalock, A., and Levy, S.: Tuberculous Pericarditis, *J. Thoracic Surg.* 7: 132, 1937.
9. Burwell, C. S., and Flickinger, D.: Obstructing Pericarditis, *Arch. Int. Med.* 56: 250, 1935.
10. Burwell, C. S., and Strayhorn, W. D.: Concretio Cordis, *Arch. Surg.* 24: 106, 1932.
11. Burwell, C. S., and Blalock, A.: Chronic Constrictive Pericarditis, *J. A. M. A.* 110: 265, 1938.

12. Feil, H., and Rossman, P. L.: Electrocardiographic Observations in Cardiac Surgery, *Ann. Int. Med.* 13: 402, 1939.
13. Mautz, F. R.: Reduction of Cardiac Irritability by the Epicardial and Systemic Administration of Drugs as a Protection in Cardiac Surgery, *J. Thoracic Surg.* 5: 612, 1936.
14. Beck, C. S., and Mautz, F. R.: The Control of the Heart Beat by the Surgeon, *Ann. Surg.* 106: 525, 1937.
15. Stewart, H. J., and Heuer, G. J.: Measurements of the Circulation in Chronic Constrictive Pericarditis Before and After Resection of the Pericardium, *N. Y. State J. Med.* 39: 2183, 1939.

THE SPA TREATMENT OF THROMBOANGIITIS OBLITERANS

T. J. FATHERREE, M.D., AND CECIL HURST, M.D.

SOAP LAKE, WASH.

THE town of Soap Lake, Wash., is unique with regard to the number of its citizens who have thromboangiitis obliterans. An unofficial report of the 1940 census credits Soap Lake with a population of 619, and between the months of January and July, 1940, inclusive, thirty-four persons with thromboangiitis obliterans were residing at Soap Lake. Thus, during this period, there was approximately one person with this uncommon disease to every eighteen residents of the town. This high incidence of thromboangiitis obliterans is explained by the fact that the town of Soap Lake is situated on the shores of a mineralized body of water known as Soap Lake, which has acquired a degree of popularity as a spa which influences thromboangiitis obliterans favorably. In recent years many persons with this disease have come to Soap Lake with the hope of obtaining relief by taking baths in the lake, and drinking its mineral water, and some of these people have remained as residents of the town.

In 1939, the State of Washington founded the McKay Memorial Research Hospital for the purpose of studying the problem of thromboangiitis obliterans, with particular reference to the therapeutic effect of the water of Soap Lake and the climate of the Soap Lake vicinity on this disease. In order to throw as much light as possible on this problem, we have made a study, consisting of careful historical records and physical examinations, of the patients with thromboangiitis obliterans who reside at Soap Lake. It was felt that such a study should show whether or not the patients might have received any considerable benefits as a result of this type of therapy and should thus tend to clarify the question which has been raised concerning the effectiveness of the spa treatment of thromboangiitis obliterans at Soap Lake. The results of this study constitute the basis of this report.

Soap Lake, which is approximately 864 acres in area, is situated at the mouth of the Grand Coulee, in the Walla Walla Plateau region of central Washington, a part of the basin of the Columbia River. The elevation is approximately 1,065 feet above sea level. A summary of a chemical analysis of the surface water of Soap Lake, made in March, 1939, by Newhall,¹ Chemical Engineer for the Washington State Board of Health, is given in Table I.

The climate² of the Soap Lake region throughout spring, summer, and fall is characterized by much sunshine and scant precipitation. The humidity is comparatively high in the winter, whereas in the warmer

From the McKay Memorial Research Hospital, Soap Lake, Washington.
Received for publication Oct. 23, 1940.

TABLE I

	PARTS PER MILLION	PER CENT SOLIDS
Sodium	13,836.95	38.04
Carbonate	7,000.00	19.24
Sulphate	6,572.00	18.07
Chloride	4,437.00	12.20
Bicarbonate	4,280.00	11.77
Silica	74.00	0.20
Magnesium	52.40	0.14
Potassium	36.37	0.10
Organic nitrogen	33.10	0.09
Calcium	7.27	0.02
Oil (ichthyol-like)	29.90	0.08

Aluminum, iron, copper, rubidium, lithium, and fluoride were detected in minute amounts.

portion of the year it is moderate to low, and, on summer afternoons, it is generally from very low to extremely low. The winter temperatures are at times quite low, whereas the summer temperatures frequently reach very high levels. Generally speaking, from May through September the days are bright, hot, and dry. However, during the late fall, winter, and early spring these conditions do not prevail, and there is likely to be a considerable amount of cold and dampness, with a less abundant supply of sunshine.

The treatment used by the patients included in this study consisted of baths in the water of Soap Lake, drinking the lake water, varying amounts of rest and exposure to the sun, and daily dressings of the ulcerative and gangrenous lesions by the patients themselves. Baths were taken in the lake proper during the hot summer months, and as warm tub baths for periods of twenty to thirty minutes. In addition, foot soaks in the lake water were frequently used for the treatment of ulcerative and gangrenous lesions. It should be emphasized that, aside from the prescribing of narcotics and the performance of amputations by physicians, these patients received practically no medical supervision.

RESULTS OF STUDY

At the time of this study, which was made during the months of January to July, 1940, inclusive, thirty-four persons with thromboangiitis obliterans were residing at Soap Lake. We obtained the cooperation of thirty-two of these for the purpose of this investigation. All of the patients were men. Data on all patients with vasospastic disturbances, arteriosclerosis obliterans, and other types of peripheral vascular disease, when there was any doubt about the diagnosis, have been excluded from this report to the best of our ability.

Inquiry was made of all patients concerning the diligence with which they took the hydrotherapy under investigation, namely, bathing in, and drinking the water of Soap Lake. Thirty-one (97 per cent) of the patients stated that they had taken baths three to four times weekly, or oftener, either throughout their residence at Soap Lake, or for consider-

able periods of time after the beginning of their residence. At the time of the inquiry only three of the patients (Cases 6, 30, and 31) stated that they no longer bathed in the water of Soap Lake. However, these patients had taken daily baths for twenty-five months, twenty-seven months, and two months, respectively, before discontinuing them. Another exception (Case 8) stated that he had taken one to two baths weekly throughout his residence at Soap Lake.

Fourteen of the subjects (43.8 per cent) stated that they had drunk water from Soap Lake daily during their residence; five (Cases 6, 9, 19, 29, and 31) had drunk it daily for periods of twenty-five months, two weeks, twelve months, eight years, and two months, respectively, before discontinuing it entirely; three (Cases 1, 17, and 30) had drunk it daily for twelve months and afterward one to two times weekly; seven had drunk it regularly three to four times weekly throughout their residence at Soap Lake; one (Case 15) had drunk it three to four times weekly for nine years, and subsequently one to two times weekly; one had drunk it one to two times weekly throughout his residence; and one, just occasionally.

Thus, it is apparent that, on the whole, the patients took the hydrotherapy with a fair degree of consistency and diligence.

The economic status of these thirty-two persons during their residence at Soap Lake was as follows: Eight were self-supporting; five depended upon insurance payments for a part of, or their entire, support; ten were veterans of the World War and received governmental support; eight received aid from the county welfare department and were dependent either partly or entirely upon this aid for their support; and one was supported by his family.

THE FACTORS OF AGE, RACE, AGE AT ONSET OF SYMPTOMS, DURATION OF SYMPTOMS PRIOR TO BEGINNING RESIDENCE AT SOAP LAKE, PERIOD OF RESIDENCE AT SOAP LAKE, AND THE EXTENT OF SMOKING

The youngest patient was 27 years of age and the oldest, 56; the average age of all the patients was 42.28 years. It is of interest that none of the patients was Jewish. The youngest age at onset of symptoms was 19 years, the oldest, 49, and the average, 29.41 years. The shortest period of duration of symptoms prior to the beginning of the patient's residence at Soap Lake was one year, the longest, twenty-two years, and the average, ten years. The time of residence at Soap Lake varied from seven months to ten years, and the average was 2.67 years. Some of the patients were away from Soap Lake during their period of residence for varying lengths of time, as follows: Case 1, seven months; Case 10, two months; Case 18, four months; Case 25, one month; Case 26, four months; Case 27, twenty-eight months; Case 29, forty months; Case 31, twenty months; and Case 32, six months.

Smokers were classified as follows: Grade I, five cigarettes, or less, daily; Grade II, five to fifteen cigarettes daily; Grade III, fifteen to twenty-five cigarettes daily; Grade IV, more than twenty-five cigarettes daily. All of the patients were smokers at one time or another. Before beginning their residence at Soap Lake, two (6.3 per cent) were Grade I smokers, nine (28.1 per cent) were Grade II smokers, eighteen (56.2 per cent) were Grade III smokers, and three (9.4 per cent) were Grade IV smokers. One (Case 10) quit smoking six years, and another (Case 24) eighteen months, prior to beginning residence at Soap Lake. Neither of these patients resumed smoking. During their Soap Lake residence, four patients, 12.5 per cent) were Grade I smokers, seven (21.9 per cent), Grade II, sixteen (50 per cent), Grade III, and one (3.1 per cent), Grade IV, while four of the patients (Cases 2, 10, 18, and 24) did not smoke at all.

THE FACTOR OF OCCUPATION

Originally, twenty-two (69 per cent) of these patients were engaged in occupations requiring manual labor, and ten (31 per cent) were engaged in sedentary occupations. Twelve patients (37 per cent) were employed at their usual occupations until the time of their arrival at Soap Lake; seven (22 per cent) had modified their occupations on an average of 3.2 years before coming to Soap Lake; and thirteen (41 per cent) had given up their occupations completely on an average of 3.9 years before coming to Soap Lake. On the other hand, during their residence at Soap Lake only five patients (16 per cent) were engaged in their usual occupation, nine (28 per cent) in a modified type of occupation, and eighteen (56 per cent) did no work at all. In all instances a modification of occupation resulted in work requiring less physical activity.

THE OCCURRENCE OF SUPERFICIAL THROMBOPHLEBITIS BEFORE AND DURING SOAP LAKE RESIDENCE

Twenty-one patients (66 per cent) had recurrent attacks of superficial phlebitis prior to their residence at Soap Lake, and twenty (62.5 per cent) had recurrent attacks during their Soap Lake residence. Of the twenty-one patients who had phlebitis prior to living at Soap Lake, sixteen (76 per cent) continued to have recurrent attacks during their residence at Soap Lake. Of the sixteen patients who continued to have recurrent attacks of phlebitis while residing at Soap Lake, nine had phlebitis at the same rate of frequency, one had it more often, and six, less frequently. Of the eleven patients who had no phlebitis prior to residence, four developed phlebitis after coming to Soap Lake. Seven of the patients who had no phlebitis prior to coming to Soap Lake did not develop it while residing there. Of the twenty patients who had phlebitis while residing at Soap Lake, ten (50 per cent) had recurrent attacks over a period constituting 90 to 100 per cent of the time spent

TABLE II
PATIENTS WITH THROMBOANGITIS OBLITERANS RESIDING AT SOAP LAKE, WASHINGTON

CASE NO.	AGE (YEARS)	RACE	AGE AT ONSET (YEARS)	DURATION PRIOR TO SOAP LAKE RESIDENCE (YEARS)	TIME OF RESIDENCE AT SOAP LAKE (MONTHS)	SMOKING							
						BEFORE SOAP LAKE RESIDENCE				DURING SOAP LAKE RESIDENCE			
						I	II	III	IV	I	II	III	IV
1	36	German-English	29	5	26			X				X	
2	45	French	32	12	12				X				
3	43	German-French-Irish	29	11	37			X				X	
4	56	French-American	49	4	32		X			X			
5	50	German-Irish	30	17	37		X						
6	44	Scotch	19	22	37			X				X	
7	48	English	27	18	33			X				X	
8	42	English	27	14	8			X				X	
9	40	German-English	28	11	10			X		X			
10	40	Irish	33	6	12			X					
11	43	American	29	11	33		X			X		X	
12	27	Scotch-Irish	19	5	39				X				
13	47	Scotch-Irish	44	1	32				X		X		X
14	36	English	30	3	35		X						
15	51	English-Irish	31	10	120			X				X	
16	43	Scotch-Irish	31	11	16			X				X	
17	48	Irish	26	18	52			X				X	
18	43	Scotch	41	1	16				X				
19	34	American	24	1	35			X				X	
20	34	German-Scotch	26	6	21			X				X	
21	45	Scotch-Irish	29	14	21			X				X	
22	47	German-Irish	39	7	12			X				X	
23	41	French-English	31	8	30	X				X			
24	34	American	26	7	8			X					
25	47	German-French	27	19	13			X				X	
26	46	Irish	23	21	26		X				X		
27	40	German-English	27	9	48		X				X		
28	37	American	29	7	7			X				X	
29	47	American	25	12	117		X			X	X		
30	45	American	31	11	36		X			X	X		
31	46	American	26	17	36		X					X	
32	28	Norwegian	24	1	31	X				X			

Any one case number refers to the same patient in all tables.

TABLE III

THE OCCURRENCE OF PHLEBITIS IN PATIENTS WITH THROMBOANGITIS OBLITERANS BEFORE AND DURING RESIDENCE AT SOAP LAKE

CASE NO.	PRIOR TO SOAP LAKE RESIDENCE		DURING SOAP LAKE RESIDENCE		FREQUENCY OF ATTACKS AS COMPARED WITH FREQUENCY PRIOR TO SOAP LAKE RESIDENCE		
	RECURRENT ATTACKS OF PHLEBITIS		PERIOD OF TIME DURING WHICH ATTACKS OCCURRED (YEARS)	TIME OF RESIDENCE AT SOAP LAKE PRIOR TO MOST RECENT ATTACK (MONTHS)	RECURRENT ATTACKS OF PHLEBITIS		
	PRESENT	ABSENT			PRESENT	ABSENT	
1	x	x	11	35			
2	x		2	32			x
3				25			
4		x	8	31			
5	x		6	33			
6	x		NS	8			
7	x						
8		x	NS				
9	x						
10		x	4	15			
11	x		4½	27			
12	x			26			
13							
14		x					
15	x	x	1	114			
16	x		11	12			
17	x		18	51			
18							
19	x	x	NS				
20	x		6	16			
21	x		NS	15			
22	x		7	11			
23	x		9	30			
24	x		7				
25							
26	x		1	15			
27		x					
28	x		7	7			
29	x		NS				
30	x		2	34			
31		x		24			
32		x					

NS, Not stated in record of case.

at Soap Lake, two (10 per cent), 80 to 89 per cent, three, 70 to 79 per cent, three, 60 to 69 per cent, one, 50 to 59 per cent, and one over a period constituting 40 to 49 per cent of the time spent at Soap Lake, all dating from the beginning of residence. Thus, fifteen (75 per cent) of the patients had phlebitis for periods greater than 69 per cent, whereas only five (25 per cent) had phlebitis for periods less than 69 per cent of the time spent at Soap Lake, dating from the beginning of their residence.

THE OCCURRENCE OF ULCERATION AND GANGRENE AND THE INCIDENCE AND
TIME OF HEALING OF THESE LESIONS BEFORE AND DURING
SOAP LAKE RESIDENCE

For the purpose of simplification, ulceration and gangrene are spoken of here as occurring in attacks. An attack of ulceration with or without gangrene was defined arbitrarily as a lesion consisting of either ulceration, gangrene, or both, on one extremity, or one or more lesions at the same time on the same extremity. Thus, if one toe became gangrenous or ulcerated and subsequently another area of the same foot became ulcerated or gangrenous before the initial lesion had healed or had led to amputation, the entire process to the point of healing or amputation was considered as a single attack. However, if two extremities were involved at one time, the lesions were considered as constituting two attacks. Postoperative ulceration or gangrene which failed to heal after a major amputation, so that reamputation was necessary, or persisted for a period of more than three months, was considered as constituting an attack different from the lesion for which the amputation was performed. However, failure of the lesion to heal after a minor amputation was not considered an attack different from that for which the amputation was performed. Twenty-nine patients (91 per cent) had a total of 125 attacks of gangrene with or without ulceration prior to coming to Soap Lake, whereas seventeen patients (53 per cent) developed a total of thirty-seven attacks of gangrene with or without ulceration during their Soap Lake residence. Inasmuch as the average duration of the disease prior to Soap Lake residence was ten years, and the average time of residence of these patients at Soap Lake was 2.67 years, the patients obviously had more time to develop ulceration and gangrene before their arrival at Soap Lake than during their stay there. Hence, the development of ulceration and gangrene was computed on the basis of the average number of attacks per patient per average number of years of duration of symptoms for the periods before and during Soap Lake residence. This computation was made, first, by dividing the total number of attacks of gangrene with or without ulceration in a given period by the total number of patients in the series, for the purpose of obtaining the average number of attacks of ulceration with or without gangrene per patient. This figure was then divided by the figure repre-

senting the average duration, in years, of the period being investigated. The result represents the average number of attacks of ulceration with or without gangrene per patient per average number of years of duration of the period being investigated. When computed on this basis, it was found that the average number of attacks per patient per average number of years of duration of the disease prior to Soap Lake residence was 0.39, whereas the figure calculated on the same basis for the duration of residence at Soap Lake was 0.43.

Of the twenty-nine patients who had 125 attacks of ulceration with or without gangrene prior to the beginning of Soap Lake residence, fifteen recovered from thirty-six attacks (29 per cent) prior to coming to Soap Lake, whereas eighty-nine attacks (71 per cent) which developed in twenty-five cases prior to residence at Soap Lake failed to heal, and either led to amputation or were still present when the patients came to Soap Lake. Of the fifteen patients with one or more attacks of ulceration with or without gangrene from which they recovered, we obtained data on fourteen concerning how long it took to recover; the average time was 4.3 months.

Of the seventeen patients who had a total of thirty-seven attacks of ulceration with or without gangrene while residing at Soap Lake, thirteen recovered from twenty-four attacks (65 per cent) in an average time of 5.8 months, whereas thirteen attacks (35 per cent) in nine cases continued and either led to amputation or were still present when the patients were interviewed by us.

The time of appearance of the thirty-seven attacks of ulceration after beginning residence at Soap Lake was as follows: Eight developed within the first six months; eight, within seven to twelve months; nine, within the second year; seven, within the third year; three, within the fourth year; and two, within the ninth year.

Of the twenty-five patients who developed ulceration with or without gangrene which failed to heal prior to coming to Soap Lake, eighteen had a total of twenty-five attacks on arrival. Fourteen patients recovered from seventeen attacks (68 per cent) in an average time of 8.4 months, and five patients did not recover from eight attacks (32 per cent).

THE INCIDENCE OF AMPUTATION BEFORE AND DURING SOAP LAKE RESIDENCE

The total number of patients who had had amputations, either major, minor, or both, prior to beginning residence at Soap Lake was sixteen (50 per cent). During this period there were twenty-seven major amputations in fifteen cases (47 per cent), and forty-five minor amputations in eight cases (25 per cent), making a total of seventy-two amputations in sixteen cases. The average number of major amputations per patient was 0.843, whereas the average number of major amputations per patient per average number of years of duration of the disease prior to

TABLE V
THE INCIDENCE OF AMPUTATION PRIOR TO AND DURING SOAP LAKE RESIDENCE

[illegible]

the beginning of Soap Lake residence was 0.08. In comparison to this, during their residence at Soap Lake ten patients (31 per cent) had a total of sixteen amputations. Eight patients (25 per cent) had a total of twelve major amputations, and two (6 per cent) had a total of four minor amputations. The average number of major amputations per patient during Soap Lake residence was 0.38, whereas the average number of major amputations per patient per average number of years of residence was 0.14.

The intervals between beginning residence at Soap Lake and major amputations were as follows: One patient had two major amputations during the first six months; two had amputations within seven to twelve months; two had three amputations in the second year; three had four amputations in the third year; and one had an amputation in the fourth year of residence. The minor amputations were distributed as follows: One in the first six months and three within seven to twelve months.

Of the entire group of thirty-two patients, nineteen (59 per cent) had had major amputations at the time this survey was made.

THE PROGRESS OF INTERMITTENT CLAUDICATION AT SOAP LAKE

Twenty-three (72 per cent) of the thirty-two patients stated that they had had intermittent claudication on arrival at Soap Lake. During their residence, seven (30.4 per cent) improved, eleven (47.8 per cent) remained the same, five (21.7 per cent) became worse, and one patient, who did not have claudication prior to residence, developed it.

THE OCCURRENCE OF ARTERIAL OCCLUSION IN PATIENTS RESIDING AT SOAP LAKE

During the period from July, 1939, to July, 1940, we observed four patients who had an extension of their arterial occlusion between the time of the initial and subsequent examination. In August, 1939, one patient (Case 1) had normal pulsations in the popliteal and dorsalis pedis arteries on the left. In September, 1939, he developed an acute arterial occlusion, with absence of pulsation in the left popliteal and dorsalis pedis arteries. Massive gangrene of the left foot developed, necessitating amputation two weeks later. This patient had resided at Soap Lake seventeen months at the time of the acute arterial occlusion. Another patient (Case 4) was first examined March 23, 1940, at which time the pulsation in the right radial artery was normal. The pulsation in the left ulnar artery was graded II (IV representing a normal pulsation, and 0, no pulsation). The popliteal artery on the left was graded II. The patient was subsequently examined May 25, 1940, after he had resided thirty-one months at Soap Lake. At this time the right radial, the left ulnar, and the left popliteal arteries did not pulsate. The history given at this time was of an acute arterial occlusion approximately one week previously, involving the left lower extremity.

Subsequently, he developed severe rest pain and gangrene of the left great toe. Another patient (Case 22) was first examined April 12, 1940, at which time the radial artery on the right did not pulsate, but the ulnar artery on the right pulsated normally. Subsequent examination, May 14, 1940, after he had resided for twenty-eight months at Soap Lake, showed absence of pulsation in the right ulnar artery. The patient subsequently developed ulceration of the right index finger. The fourth patient (Case 23) was first examined in October, 1939, at which time the left radial artery pulsated normally. When examined Dec. 13, 1939, after he had resided for five months at Soap Lake, the left radial artery did not pulsate. Subsequently the patient developed an ulcer of the left index finger.

THE OPINION OF THE PATIENTS AS TO THEIR PROGRESS AT SOAP LAKE

Twenty-five of the patients stated that they had obtained substantial symptomatic relief; five, that they had noticed no symptomatic improvement; and two, that they were undecided with regard to the question of symptomatic improvement.

COMMENT

We have presented the results of a study of thirty-two patients with thromboangiitis obliterans residing at Soap Lake for the purpose of attempting to evaluate the effectiveness of the spa treatment of this disease at Soap Lake. The opportunity for this type of study was excellent because the patients had subjected themselves to the treatment over relatively long periods of time, and had not used any other kind of treatment, and because we had opportunity to interview and examine them.

A consideration of the smoking factor, as it applied to the patients before and while residing at Soap Lake, shows that a large percentage of the patients smoked both before and after coming to Soap Lake, and, therefore, this factor could hardly be considered of importance in so far as it might have affected the comparative progress of the disease before and during residence at Soap Lake.

When the group was considered from the occupational standpoint, the conditions were somewhat more favorable during their residence at Soap Lake than they were prior to arrival, for more of them were doing no work at all, and fewer of them were engaged in their usual occupations.

Perhaps the most convincing evidence against the specificity of the treatment available at Soap Lake for thromboangiitis obliterans is the data regarding the occurrence of recurrent phlebitis before and during residence at Soap Lake, and the fact that four patients had a progression of their arterial occlusion after considerable periods of residence at Soap Lake. The fact that 63 per cent of these patients continued to have phlebitis after coming to Soap Lake and that 75 per cent of the

patients who did have phlebitis had it over periods of 70 per cent or more of the time which they spent at Soap Lake indicates that the treatment available at Soap Lake does not arrest the activity of the disease.

A consideration of the ulcerative and gangrenous lesions of these patients before and after coming to Soap Lake is of interest. A computation of the rate of development of ulcerative or gangrenous lesions per patient per average number of years of duration of the disease for the periods representing the duration of the symptoms before and during Soap Lake residence indicates that the patients developed these lesions at a slightly greater rate after they came to Soap Lake. It is well appreciated that these figures imply trends, rather than mathematical exactness, because there are many factors which might influence them. However, they are of value in showing that the treatment of thromboangiitis obliterans at Soap Lake, under the conditions which have been described, does not influence appreciably the development of ulceration and gangrene.

It is of interest that, of the ulcerative and gangrenous lesions which developed in these cases before the patients came to Soap Lake, 71 per cent failed to heal prior to the beginning of residence. In contrast to this, of the twenty-five separate instances of ulceration or gangrene which were present in eighteen patients upon their arrival at Soap Lake, seventeen (68 per cent) in fourteen patients healed in an average time of 8.4 months after arrival, and eight (32 per cent) in five patients failed to heal. The lesions of three of the patients which failed to heal led to one minor and two major amputations, and the lesions of the remaining two patients were still present at the time of this survey. Furthermore, of the thirty-seven attacks of ulceration with or without gangrene which developed in seventeen patients during their residence at Soap Lake, twenty-four attacks in thirteen patients (65 per cent) healed in an average time of 3.8 months, and thirteen attacks (35 per cent) in nine patients failed to heal. The lesions of seven of the patients which failed to heal led to nine major and three minor amputations, while the lesions of two of the patients were still present at the time of the survey.

Thus, there were sixty-two attacks of ulceration with or without gangrene in twenty-four patients who were subjected to the form of treatment under consideration. Of these, forty-one (66 per cent) healed and twenty-one (34 per cent) failed to heal.

Twenty-five per cent of the patients included in this study had major amputations during their residence at Soap Lake. A computation of the number of major amputations per patient per average year of residence shows that the rate of major amputation was somewhat higher in these patients during residence than was the case prior to their residence at Soap Lake.

For comparison, it may be noted that McKittrick³ reported that 31 per cent of the patients with thromboangiitis obliterans who were admitted to the Massachusetts General Hospital from 1929 to 1939 had major amputations before leaving the hospital, and Horton⁴ stated that 15.6 per cent of the patients with thromboangiitis obliterans who were treated at the Mayo Clinic from 1907 to 1937, inclusive, had amputations at the clinic. In this connection, Silbert⁵ has stated that, before the institution of modern types of therapy, 60 per cent of the patients with ulceration or gangrene had amputations. However, Samuels⁶ reported treating more than 300 patients with thromboangiitis obliterans without having to do more than one major amputation, and Silbert reported an amputation incidence of only 6.4 per cent in a series of 687 cases in which the patients were treated with hypertonic saline intravenously.

The explanation for the popularity of Soap Lake as a spa for the treatment of thromboangiitis obliterans undoubtedly lies in the considerable percentage (66 per cent in the cases included in this study) of gangrenous and ulcerative lesions which heal while the patients are treating themselves at Soap Lake.

It is remarkable that these patients, who were practically without medical supervision, and who, for the most part, smoked excessively, progressed as favorably as they did. To what extent, if any, the spa treatment has influenced the progress of the disease is difficult to say. However, in our opinion, the frequent healing of gangrenous and ulcerative lesions at Soap Lake emphasizes the ever-present tendency that these lesions have toward healing, provided they are kept at rest, kept clean, and not subjected to meddlesome surgical procedures.

Any attempt to evaluate the beneficial effects of taking baths and foot soaks in the water of Soap Lake on the gangrenous and ulcerative lesions of thromboangiitis obliterans is hampered greatly by the fact that, practically, it is impossible to treat the lesions with this measure alone. The very nature of the lesions demands a certain amount of rest. The tendency on the part of the patient, however, is to give the major share of the credit for the healing of a lesion to the particular type of treatment which was being used when healing occurred. This tendency is not peculiar to patients, for it may be observed frequently in medical reports concerning the treatment of thromboangiitis obliterans and other chronic diseases. For instance, if patients with gangrenous and ulcerative lesions are treated with rest in bed, heat, foot soaks, and typhoid vaccine intravenously, to give a specific example, the tendency on the part of the observer, frequently, is to give the major share of the credit for any healing which occurs to the more spectacular part of the treatment, which in this instance happens to be typhoid vaccine. Specious reasoning of this type impedes rather than hastens the reasonable evaluation of therapy. The observations reported here serve, it seems to us, to emphasize the well-known but often disregarded fact

that the majority of the gangrenous and ulcerative lesions of thromboangiitis obliterans, if kept at rest, kept clean, and spared the trauma incident to ill-advised local surgical procedures, will heal of their own accord.

CONCLUSIONS

1. This study indicates that the spa treatment of thromboangiitis obliterans at Soap Lake, Washington, is not a specific treatment for this disease.

2. The ulcerative and gangrenous lesions of the patients who were studied healed in a large percentage of cases.

REFERENCES

1. Newhall, C. A.: Personal communication to the authors.
2. U. S. Dept. of Agriculture Weather Bureau: Climactic Summary of the United States. Section 2. Eastern Washington.
3. McKittrick, L. S.: The Diagnosis and Management of Chronic Obliterative Vascular Disease, J. A. M. A. 113: 1223, 1939.
4. Horton, B. T.: The Outlook in Thrombo-Angiitis Obliterans, J. A. M. A. 111: 2184, 1938.
5. Silbert, S.: Clinical Evidence Upon Which the Use of Tobacco May Be Incriminated as the Essential Cause of Thrombo-Angiitis Obliterans, S. Clin. North America 18: 389, 1938.
6. Samuels, S. S.: Gangrene Due to Thrombo-Angiitis Obliterans, J. A. M. A. 102: 436, 1934.

THE SIGNIFICANCE OF LOW VOLTAGE OF THE QRS COMPLEX IN PRECORDIAL LEADS

COMPARISON WITH LOW VOLTAGE IN LIMB LEADS

SAMUEL BELLET, M.D., AND ALFRED KERSHBAUM, M.D.
PHILADELPHIA, PA.

THE significance of low voltage of the QRS complexes in the limb leads of the electrocardiogram has been discussed by many observers.¹ There can be little question that, in many instances, low voltage complexes are a result of severe myocardial disease. However, this is by no means always so, for complexes which are definitely below the accepted limits of normal are often observed when there is only slight myocardial involvement, and even when the heart is normal. Although Willius and Killins² attributed to myocardial disease the low voltage which they found in 32 per cent of 140 cases, they feel that low voltage which is unassociated with other graphic abnormalities neither indicates serious myocardial disease necessarily, nor, *ipso facto*, is of serious prognostic import. The diagnosis of myocardial disease, although it may be suggested, cannot be made positively upon the evidence of low voltage alone.

As far as we are aware, the literature contains no study of the significance of low voltage of the QRS complexes in precordial leads. The lack of correspondence between the amplitude of different precordial leads and that of the limb leads is well recognized.^{3, 4, 5} Usually, low voltage in the limb leads, even when it results from severe myocardial disease, is accompanied by normal voltage in the precordial leads. Much less frequently have we observed that low voltage was present in both limb and precordial leads. The present study is an attempt to evaluate the factors which are responsible for this agreement, and the significance of curves in which the voltage of the QRS complexes is low in both limb and chest leads.

METHOD

For this study, twenty cases of low voltage in both limb and precordial leads, in which our studies were complete, were collected. The observations in this group were compared with those in fifty consecutive cases in which there was low voltage in the limb leads and normal voltage in the precordial leads. In addition, 300 normal subjects were examined for the possible presence of low voltage in the limb and precordial leads. Since pericardial disease, both with effusion and of the adherent type, is sometimes associated with low voltage, the electrocardiograms of seventy-seven patients with this disease were also reviewed.

From The Division of Cardiology of the Philadelphia General Hospital and the Robinette Foundation, University of Pennsylvania.

Received for publication Oct. 28, 1940.

The voltage was regarded as low when the greatest deflection of the QRS complex did not exceed 5 to 6 mm. in either direction from the isoelectric line. This is in accord with the criteria of Sprague and White,⁶ although Pardee⁷ sets the lower limit of normal as 7 mm.*

Just as one does not rely upon a single lead to establish low voltage in the limb leads, one should not rely upon a single precordial lead. All of the electrocardiograms included in our series were taken by the old method⁸ of applying the precordial electrodes, i.e., old Lead IV, V, VI† were used (Figs. 1 to 6). Therefore, in all of the cases both an anteroposterior chest lead (CB lead) and an apex to left leg lead (CF lead) were taken. The voltage was regarded as low when the amplitude of the QRS complex in all of the precordial leads did not exceed 5 to 6 mm. in either direction from the isoelectric line. How important it is to use CB and CF leads is illustrated by Fig. 2. Lead IV (or IVB reversed) is of considerable amplitude; Lead V (IVF reversed) has a voltage of only 5 mm. The above emphasizes the fact that the voltage in the precordial leads should not be regarded as low unless anteroposterior (CB leads), as well as apex to left leg (CF leads), have been taken.‡ In Figs. 3 to 6, although different precordial leads were taken, only one precordial lead (CB), that displaying the greatest amplitude, is shown.

All tracings were carefully standardized so that the string yielded a deviation of 1 cm. for each millivolt of current. Patients were either in the recumbent or sitting position while the electrocardiograms were being taken. In serial tracings on any one patient, the same position was always assumed.

OBSERVATIONS

The data on the twenty cases in which there was low voltage in both the precordial and limb leads are summarized in Table I, and show two rather striking things. The first was the fact that severe myocardial damage was present in all of the twenty cases (100 per cent), as shown by clinical examination, the electrocardiogram, and, in three instances, by necropsy studies. Eleven of the patients (55 per cent) died during the period of observation in the hospital. The second noteworthy point was the large number of instances of myocardial infarction (eleven cases, 55 per cent). Of these, infarction involving the anterior and posterior portions of the heart was present in five cases§ (25 per cent), and anterior infarction alone in six cases. The possible significance of these facts will be discussed subsequently. In the remaining cases the etiology was as follows: arteriosclerotic, five; rheumatic, two; syphilitic, one; and tuberculous pericarditis, one. Clinically manifest edema of various degrees was present in nine (45 per cent) of these cases.

In this series, seventeen patients had electrocardiographic changes which were characteristic of myocardial disease, in addition to the low

*Low voltage in the limb leads may occasionally be produced as an artifact by some fault in the electrocardiographic apparatus. We have also occasionally observed its appearance in precordial leads as a result of faulty application of the precordial electrode. We believe that neither of these factors applies in any of our cases. In most of these cases, the low voltage was observed in repeated electrocardiographic tracings over a considerable period of time.

†Lead IV is IVB reversed.⁹ Lead V is IVF reversed. In Lead VI, the left arm electrode is placed at the angle of the left scapula and the left leg electrode on the left leg.

‡In addition to CB, CR was taken. Occasionally this may be slightly greater in amplitude than CB.

§Three of these patients came to necropsy, which revealed extensive infarction involving both the anterior and posterior wall of the left ventricle.

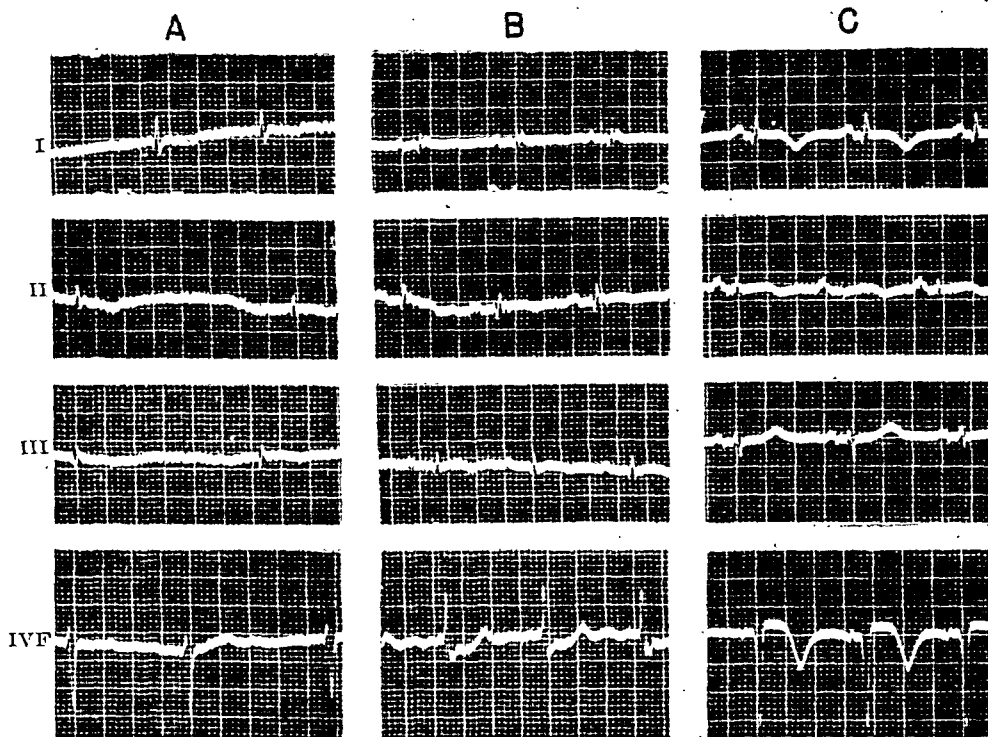


Fig. 1.—Note low voltage in limb leads, normal voltage in precordial leads. (A) A.B., aged 53. Arteriosclerotic cardiovascular disease, congestive failure with edema. (B) A.S., aged 83. Arteriosclerotic cardiovascular disease, posterior myocardial infarction, slight edema. (C) A.S., aged 70. Recent anterior infarction, no edema.

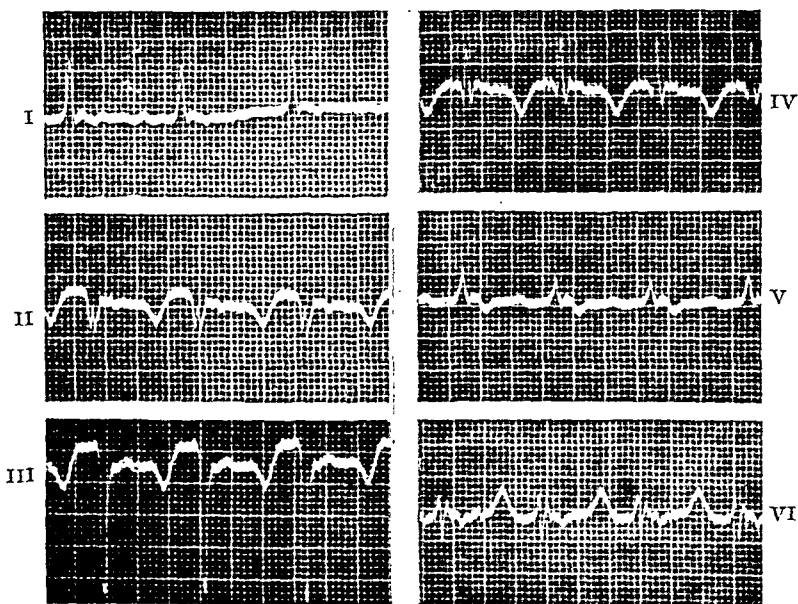


Fig. 2.—Shows the marked difference in voltage between IVB reversed (old Lead IV) and IVF reversed (old Lead V). F.S., aged 54. Anterior myocardial infarction. Note the high voltage of the QRS in Lead IV (reverse of IVB) and low amplitude in Lead V (reverse of IVF). This figure illustrates the importance of taking IVB before stating that the amplitude of the precordial lead is low.

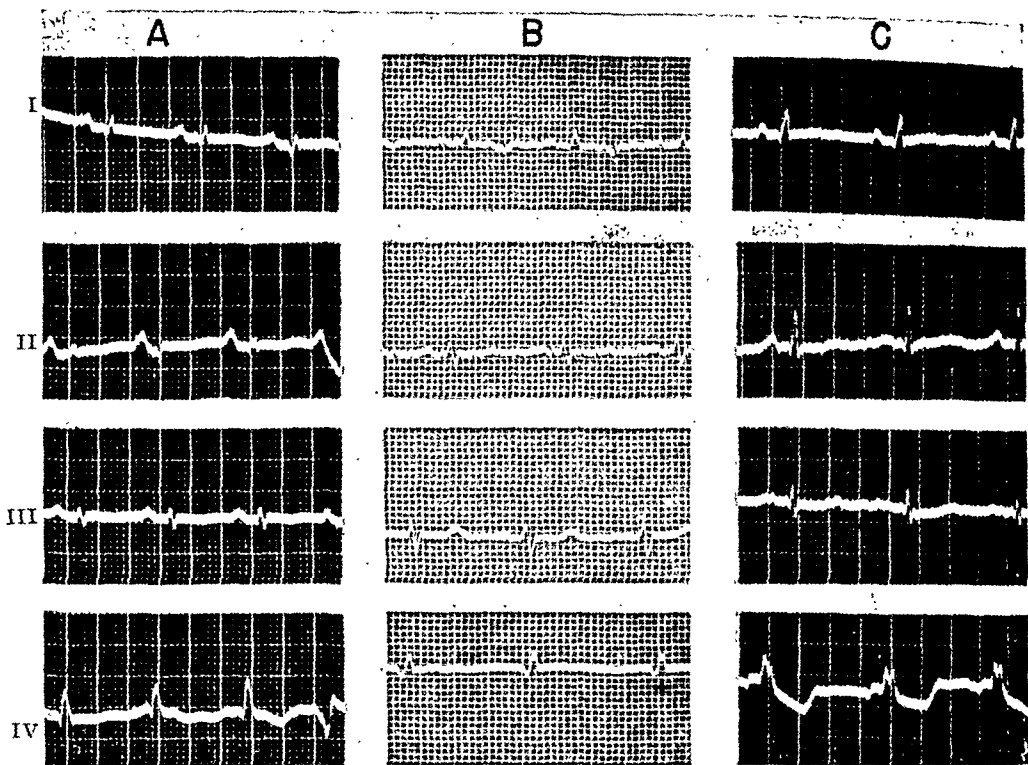


Fig. 3.—(A) Case 6: (Table I) Rheumatic heart disease, congestive failure. (B) Case 15: (Table I) Anterior myocardial infarction (chronic stage), arteriosclerotic heart disease, slight edema. (C) Case 8: (Table I) Recent anterior myocardial infarction, no edema. The precordial lead is IVB reversed (old Lead IV).

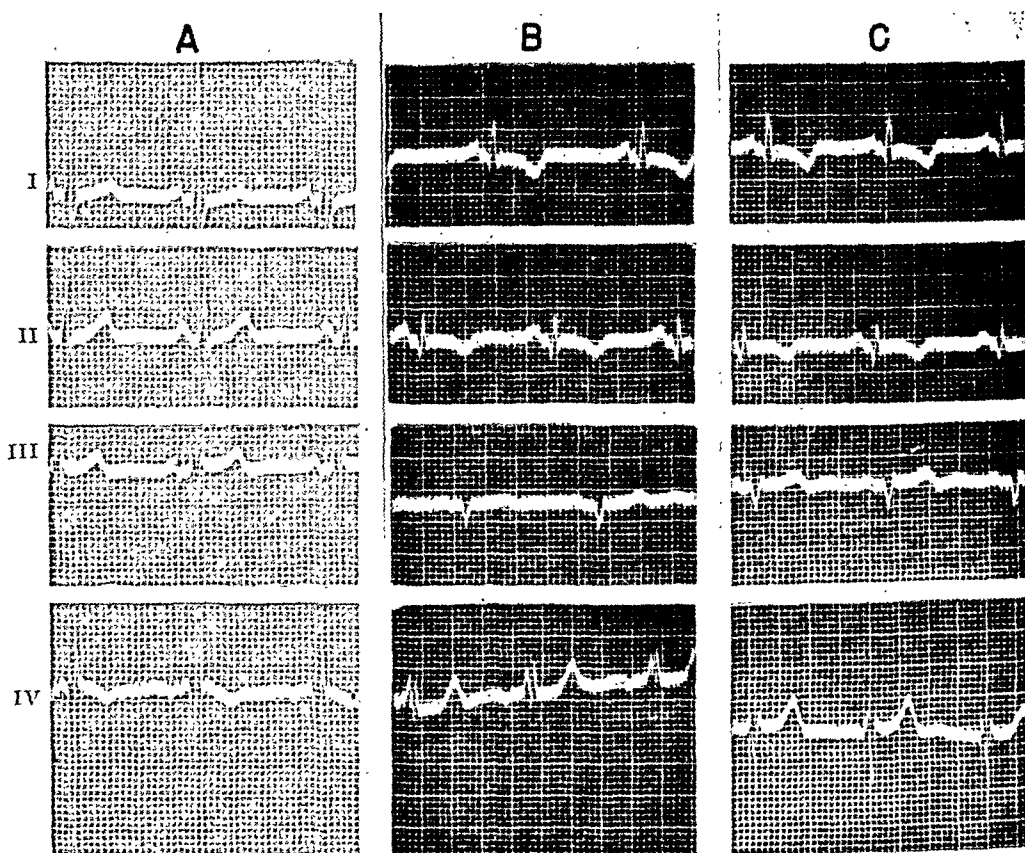


Fig. 4.—Case 2: (Table I) Male, aged 52. (A) Oct. 14, 1933. Diabetes, generalized arteriosclerosis. (B) Feb. 12, 1934. Patient developed acute coronary occlusion involving the anterior, and, later, the posterior wall of the left ventricle. Note the low amplitude in all leads, particularly old Lead IV (IVB reversed). Compare with (A). (C) Mar. 30, 1934. After his general condition had improved, some healing had taken place. Note increased voltage in Lead IV (reverse of IVB).

voltage. In the three remaining cases, the limb leads (except for low voltage) were within normal range, but in two of these there were abnormalities in the precordial leads. Therefore, in this series, electrocardiographic changes, aside from the low voltage, were observed in almost all the cases.

In an attempt to ascertain further the significance of low voltage in chest leads, we have also studied certain other groups of patients.

In Table II are shown the data on fifty patients who showed low voltage in the limb leads, but normal voltage in the chest leads.*

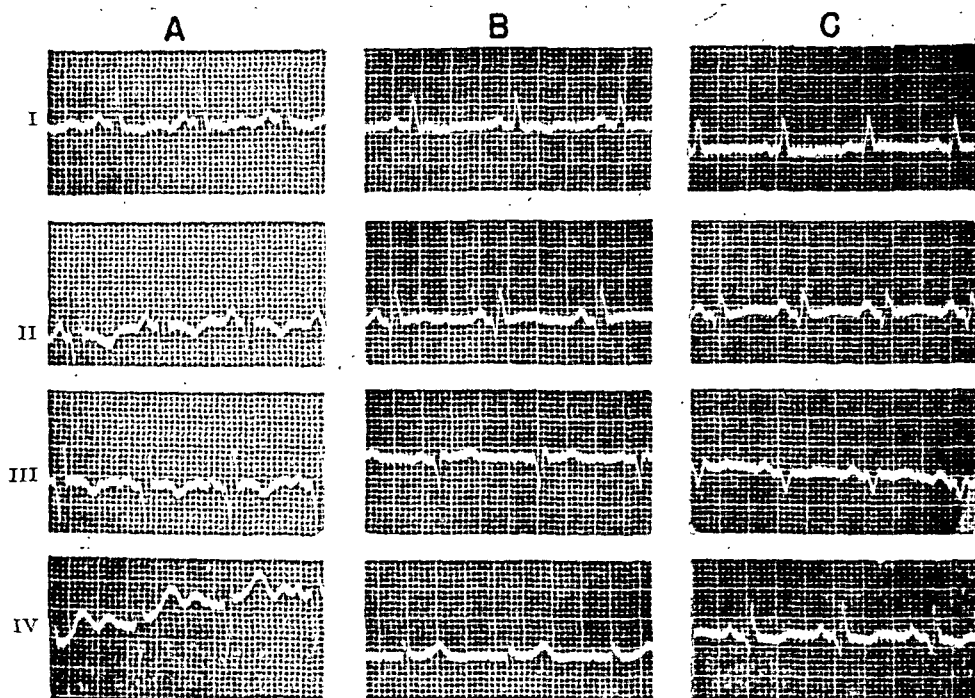


Fig. 5.—Case 16: (A) Jan. 25, 1935. Subsequent to posterior myocardial infarction. (B) April 1, 1935, two days after severe attack of precordial pain. Note low voltage in Lead IV. (C) May 29, 1936. Improvement in general condition. Note increase in voltage of QRS in Lead IVB reversed (old Lead IV). Autopsy revealed anterior and posterior infarction.

The severity of the myocardial damage in this group was much less marked than in the first. Only eighteen patients (36 per cent) had severe myocardial damage, as compared to 100 per cent in the previous group. Moreover, seventeen (34 per cent) had either normal hearts or slight myocardial damage, and fifteen (30 per cent) had a moderate grade of myocardial disease. Only thirteen patients (26 per cent) had myocardial infarction in this group, as compared to eleven (55 per cent) in the group with low voltage in both limb and precordial leads. In the group with low voltage in both limb and precordial leads, edema was

*It should be remembered that these electrocardiograms were taken on patients with suspected myocardial disease, in the medical wards. The percentage of myocardial disease in these cases of low voltage in limb leads might have been lower, had a different method of selection, such as was used in the series of Willis and Killins,² been applied.

TABLE I
SUMMARY OF CASES OF LOW QRS VOLTAGE IN BOTH DIRECT AND INDIRECT LEADS*

CASE NO.	AGE	SEX	CHANGES OTHER THAN LOW VOLTAGE	EDEMA	CARDIAC DIAGNOSIS	GRADES OF MYOCARDIAL DISEASE	OUTCOME
1	64	M	T ₁ inverted; QRS slurred and notched in all 3 leads; LAD	Slight	Arteriosclerotic heart disease. Cardiac decompensation	Severe	Improved
2	49	M	T ₁ and ₂ inverted and cove-shaped; T ₄ inverted; Q ₂ and ₃ present; LAD; R ₄ absent	No	Arteriosclerotic heart disease. Chronic ant. and recent post. myocar. infarc.	Severe	Improved
3	37	F	T flattened in all 3 leads; ventric. extrasystoles	Moderate	Rheumatic heart disease. Cardiac decompensation	Severe	Died
4	42	M	T ₁ and ₂ inverted; LAD	Slight	Syphilitic heart disease. Cardiac decompensation.	Severe	Improved
5	74	F	T ₁ and ₂ flat; S-T ₁ and ₂ depressed; S-T ₂ elevated; Q ₂ and ₃ present; LAD; R ₄ absent	Marked	Arteriosclerotic heart disease. Chronic ant. myocar. infarc. Acute post. myocar. infarc.	Severe	Died (autopsy)
6	28	M	T flat in all leads; frequent ventric. extrasystoles	Marked	Rheumatic heart disease. Cardiac decompensation	Severe	Died
7	60	M	T ₁ and ₂ inverted; LAD; R ₄ absent	Marked	Arteriosclerotic heart disease. Cardiac decompensation. Chronic ant. myocar. infarc.	Severe	Died
8	65	M	T ₁ flat; S-T ₁ elevated; S-T ₄ elevated; R ₄ absent	No	Arteriosclerotic heart disease. Acute ant. myocar. infarc.	Severe	Improved
9	62	M	Q present in all 3 leads; S-T ₄ elevated; R ₄ absent	No	Arteriosclerotic heart disease. Acute ant. myocar. infarc.	Severe	Died
10	64	M	T flat in all 3 leads	Moderate	Tuberculous pericarditis. Congestive failure	Severe	Improved

11	61	M	T ₁ inverted; T ₄ large and inverted; R ₄ absent	No	Arteriosclerotic heart disease. Acute and chronic myocar. infarc.	Severe	Improved
12	66	M	T ₂ and ₃ inverted; S-T ₁ elevated; S-T ₄ elevated; R ₄ absent	No	Arteriosclerotic heart disease. Acute ant. myocar. infarc.	Severe	Died
13	67	M	T ₂ and ₃ inverted; S-T ₁ depressed; S-T ₄ elevated; R ₄ absent	No	Arteriosclerotic heart disease. Chronic post. myocar. infarc. Acute ant. myocar. infarc.	Severe	Died (autopsy)
14	53	M	T flat in all leads; S-T ₂ and ₃ depressed; PR interval prol. (0.24 sec.)	No	Arteriosclerotic heart disease	Severe	Died
15	39	M	T ₁ inverted; T ₄ slightly inverted; LAD; R ₄ small	Slight	Arteriosclerotic heart disease. Cardiac decompensation. Chronic ant. myocar. infarc.	Severe	Died
16	53	M	T ₁ inverted; T ₂ flat; T ₄ inverted; Q ₂ and ₃ present; R ₄ absent	No	Arteriosclerotic heart disease. Chronic post. myocar. infarc. Acute ant. myocar. infarc.	Severe	Died (autopsy)
17	61	M	T flat in all leads; S-T ₁ and ₂ depressed; ventric. extrasystoles; PR prol. (0.24 sec.)	Moderate	Arteriosclerotic heart disease. Cardiac decompensation	Severe	Improved
18	50	F	T ₁ and ₂ low; Q ₃ present	No	Arteriosclerotic heart disease.	Severe	Improved
19	62	M	T ₁ flat; S-T ₄ elevated; Q ₃ present; R ₄ absent	No	Arteriosclerotic heart disease. Chronic post. myocar. infarc. Acute ant. myocar. infarc.	Severe	Improved
20	62	M	T ₁ flat; S ₂ prominent; LAD	No	Arteriosclerotic heart disease	Severe	Died

*The description of the change in the precordial leads is given according to the new method of applying the electrodes.⁹

TABLE II

CARDIAC CONDITIONS IN 50 CONSECUTIVE CASES OF LOW VOLTAGE IN LIMB LEADS
WITH NORMAL VOLTAGE IN PRECORDIAL LEADS

	CASES	
Arteriosclerotic heart disease (except acute coronary occlusion)	21	(42 per cent)
Acute coronary occlusion	12	(25 per cent)
Rheumatic heart disease	4	(8 per cent)
Syphilitic heart disease	1	(2 per cent)
Congenital heart disease	1	(2 per cent)
Pericarditis	5	(10 per cent)
Normal heart	5	(10 per cent)

observed clinically in nine cases (45 per cent) ; in the group with low voltage only in the limb leads, it was observed in thirty cases (60 per cent).

Since pericarditis, especially with effusion, is occasionally associated with low voltage of the QRS complex,¹⁰ the electrocardiograms of seventy-seven patients with pericardial disease of various types and etiologies were studied from the standpoint of voltage (Table III).

TABLE III

VOLTAGE OF THE QRS COMPLEX IN 77 CASES OF PERICARDIAL DISEASE

<i>Normal voltage of QRS in limb and precordial leads</i>	
Pericardial effusion (moderate)	21 cases
Other types of pericardial disease	37 cases
<i>Low voltage in limb leads, normal voltage in precordial leads</i>	
Pericardial effusion (moderate)	7 cases
Other types of pericardial disease	11 cases
<i>Low voltage in limb and precordial leads</i>	
Tuberculous pericarditis with effusion, and thickened pericardium	1 case

From the figures in Table III, it is apparent that pericardial effusion which is moderate in degree (approximately 500 c.c.) is not, per se, a cause of low voltage in the limb leads. Of fifty-eight patients with pericardial disease who showed normal voltage, twenty-one (36 per cent) had effusion, whereas of eighteen cases of low voltage in the limb leads with normal voltage in the precordial leads, pericardial effusion was present in only seven (38 per cent). In a total of twenty-nine cases of pericardial effusion, low voltage was present in eight, or 27 per cent ; in some of these, other factors, e.g., peripheral edema, were present, and may have had a part in lowering the voltage.

The low voltage in both limb and precordial leads in the single case of tuberculous pericarditis was probably caused by the markedly thickened, adherent pericardium. The effusion was slight, loculated, and limited to the lower right portion of the pericardial sac.

Also, for purposes of comparison, we examined the electrocardiograms of 300 normal college students. In none was there low voltage of the QRS complexes in either the limb or precordial leads.

The data presented above indicate that although low voltage in the limb leads alone may be observed when the heart is either normal or

diseased, the presence of low voltage in both the precordial and limb leads is almost always associated with considerable myocardial damage.

DISCUSSION

Factors That Affect the Voltage of Limb Leads.—The voltage of the QRS complex is, of course, primarily dependent upon the electromotive force developed by the contracting heart muscle. As registered in the electrocardiogram, however, the voltage of these waves is a resultant of the difference in potential of tissue underneath two electrodes which are quite widely separated from each other, and sometimes distant from the heart. Although a deficiency in electromotive force incident to heart disease may undoubtedly be a cause of low voltage, it is quite obvious that many other factors may play a part, even when the electromotive force at its point of origin, the heart, may be quite normal.

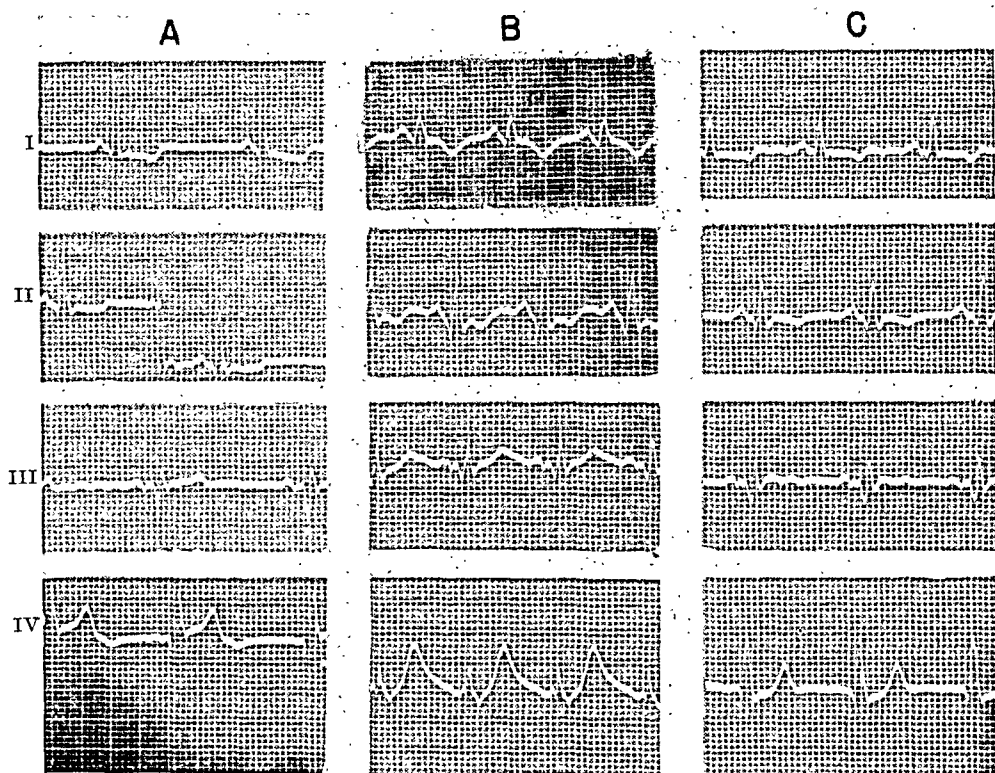


Fig. 6.—Case 11: (A) Oct. 19, 1936. History of old infarction. (B) Nov. 7, 1936. Patient experienced an attack of precordial pain. Diagnosed anterior infarction. Note diminution of voltage of QRS in Lead IVB reversed (old Lead IV). This is smaller than that noted in the limb leads.* (C) Nov. 17, 1936. With improvement, voltage has increased.

*In a few cases, as in Fig. 6 (B), we have noted a slightly lower voltage in the precordial than in the limb leads. This is apparently infrequent.

Eyster and his co-workers¹¹ and Katz and his co-workers^{12, 13} have shown that the current produced by the heart is not conducted uniformly to the surface. Some regions of the heart which are in contact with good conductors have an advantage over those portions which are not. For example, Katz, et al.,¹⁴ in summarizing their view on this subject, state that the caudad regions of the right auricle, right ventricle,

and left ventricle, and those in contact with the posterior paravertebral muscle mass will have a greater effect on the standard three-lead electrocardiogram; the portions of the heart in contact with the anterior chest wall will have a less important influence because they are surrounded by lung which is so thick that little current is conducted from this region.

In certain cases, as pointed out by Wilson,¹⁵ low voltage in the limb leads may be accidental, and be caused by the fact that the potential differences produced by one part of the heart are almost exactly neutralized by those produced in other parts. Wolferth and Wood¹⁶ believe that the limb lead voltage may be low as a result of neutralization of potentials at the surface of the body.

Voltage variations in the normal subject may be caused by many additional factors, e.g., the habitus of the individual, differences in the position and shape of the heart, the relation between the size of the heart and the size of the thoracic cage, and obesity. These factors could all be operative in entirely healthy persons; they offer a fairly satisfactory explanation of low voltage in the limb leads of persons with essentially normal hearts.

There are a number of pathologic states that might further affect the voltage of the QRS complexes.

Factors Which Modify Voltage of Limb Leads in Pathologic States.—In addition to the factors which tend to modify the voltage in the normal subject, the voltage in the presence of myocardial damage will apparently be affected in two chief ways: (a) by a modification in the source of potential, the heart, and (b) an alteration in the conduction of the heart current to the surface of the body.

An alteration in the electrical potential produced in the heart could be the result of disease of the heart muscle. An alteration in the conduction to the surface of the body of the current produced in the heart could result from a modification of the structures that normally surround the heart and act as conductors of its current. Among these are (a) air containers, which are poor conductors,^{15, 17} (b) fluid, which, because it is a good conductor, will shunt the heart current so that a smaller amount will reach peripherally-placed electrodes,^{13, 15} and (c) solid structures; thick adhesions, which are relatively avascular, will further insulate the heart, but pneumonic consolidation should act as a good conductor.^{5, 14}

In any event, we often encounter low voltage of the QRS complexes in association with massive pericardial effusion, air in the pericardium, thick adhesions around the heart, pneumonic consolidation, edema of the lung, pleural effusion, pneumothorax, generalized peripheral edema, emphysema, dehydration, and conditions associated with profound disturbances of the electrolyte content of the blood.

A combination of these factors, cardiac as well as extracardiac, may operate to produce low voltage in a given case.

Low Voltage in Chest Leads.—The various factors which may contribute to the production of low voltage in indirect leads do not apparently affect chest leads. Although low voltage may be observed in the limb leads of normal subjects, the precordial leads show normal voltage. Even in the presence of myocardial disease, one generally finds normal voltage in the chest leads when the voltage in the limb leads is notably low. As we have stated, we were able to collect only twenty well-studied instances in which the voltage in the chest lead was low.

In precordial leads, the form of the electrocardiogram depends upon factors other than those which affect limb leads. In the former, the exploring electrode is much closer to the heart, and therefore registers curves which more closely resemble the electrogram.

Although most of the factors mentioned above will tend to produce low voltage in the limb leads, few of them affect the voltage of the precordial leads. By placing the electrode over the precordium, the factors of edema, pleural effusion, pericardial effusion, etc., interfere little with the registration of the voltage.

Experimentally, Goodman¹⁸ has shown that edema, unless it is present in the subcutaneous tissues of the chest region, will not affect the voltage of the QRS complexes of the precordial leads. Clinically, edema seldom involves this region. The only other factor which is likely to affect the conduction of the heart current in precordial leads is the presence of fluid or abnormal air-containing structures between the heart and the anterior chest wall; the latter is a condition that is certainly rare. That precordial lead voltage may be affected by bilateral, massive pleural effusion is illustrated by the following case: In a patient 59 years of age, with severe degenerative heart disease, low voltage was present in the limb leads and precordial leads ($CF_{3, 4, 5}$, $CR_{3, 4, 5}$, $CB_{3, 4, 5}$). On removal of fluid from the right and left pleural sacs (30 oz.), the voltage in the precordial leads changed from 2 mm. to 5 mm. This change was recorded only in the CB and CR leads.

Since the transmission to the chest wall of the current produced in the heart is usually good, apparently the main factor which is likely to cause low voltage in the precordial leads is a decrease in the voltage produced by the heart muscle as a result of severe myocardial disease involving relatively large portions of the myocardium. This would explain the extremely low voltage in these leads in cases of anterior and posterior infarction, and the high incidence of severe myocardial disease in the group of patients reported here. That this need not be a permanent condition is illustrated in Fig. 5; in this case, anterior infarction superimposed upon an old posterior infarction resulted in low voltage. With healing of the infarct, the voltage again became normal.

If this concept is correct, it would help to establish three important points: (a) The factors which tend to produce low voltage in the limb leads do not necessarily affect the voltage of the precordial leads. (b) Low voltage in the precordial leads is usually the result of inherent

disease of the heart muscle; it is infrequently the result of extracardiac factors.* (c) Low voltage in the precordial leads is almost always associated with a severe grade of myocardial damage.

SUMMARY AND CONCLUSIONS

Of twenty patients who had low voltage in both the precordial and limb leads, all showed evidence of severe myocardial damage. In this group there were eleven cases of myocardial infarction, in five of which there was involvement of both the anterior and posterior wall of the left ventricle. The severity of myocardial disease was considerably less in a group of fifty consecutive cases in which the voltage was low in the limb leads and normal in the precordial leads. There were no cases of combined anterior and posterior infarction in this group. The incidence of low voltage in pericardial disease, both with and without effusion, is mentioned for comparison. No instances of low voltage were observed in a control group of 300 students.

One should not rely upon a single precordial lead for a diagnosis of low voltage. In addition to the CF leads (3, 4, 5), CB and CR leads should be taken.

The factors responsible for normal voltage and their modifications in various diseases are discussed. Since low voltage in the precordial leads is the result of factors other than those that produce it in the limb leads, the combination of low voltage in both is a more certain evidence of myocardial disease than the latter alone.

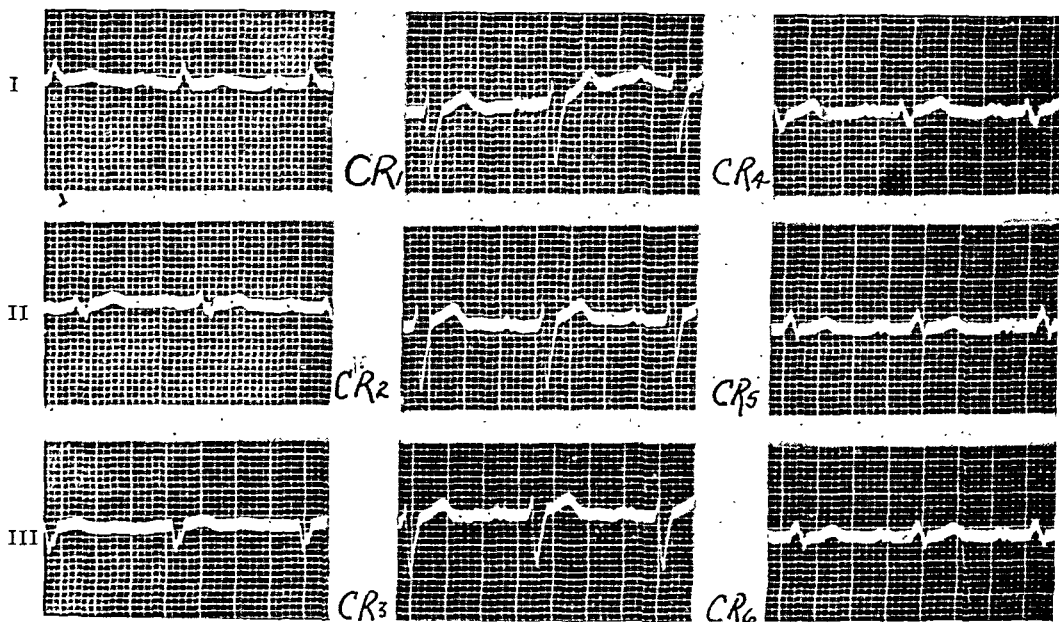


Fig. 7.—Low voltage in some chest leads with normal voltage in others. In the limb leads and in the generally used chest leads, CR₃, ₄, and ₅, the voltage is low. It is normal, however, in chest leads CR₁, ₂, and ₃. It is our opinion that the chest lead voltage should not be called "low" in such a tracing.

*In our series we have encountered but one case, mentioned above, in which the low voltage in the precordial leads was, to some degree, the result of massive pleural effusion; some of the fluid was probably situated between the heart and anterior chest wall. In this instance, severe myocardial disease was also present.

ADDENDUM

Since this paper was accepted for publication, another paper dealing with the same subject has been published by Leach, Reed, and White (*American Heart Journal* 21: 551, 1941). The difference in the conclusions expressed in the two papers may, in our opinion, result from the fact that Leach, Reed, and White used only one chest lead, so far as we can judge, whereas we used several. It has been our experience that one chest lead (frequently a conventionally used one) may yield low voltage curves, whereas chest leads from other precordial areas may give curves of normal voltage (Fig. 7). Such instances we have not considered to be examples of low chest lead voltage. It is our opinion that the voltage of the chest leads can be considered to be low only after it had been shown to be present in several chest leads.

REFERENCES

1. (a) Oppenheimer, B. S., and Rothschild, M. A.: The Value of the Electrocardiogram in the Diagnosis and Prognosis of Myocardial Disease, *Tr. A. Am. Phys.* 39: 247, 1924.
- (b) White, P. D., and Burwell, S. C.: The Clinical Significance of Changes in the Form of the Electrocardiogram, *Med. Clin. N. Amer.* 4: 1839, 1920-1921.
- (c) Clerc, A., and Bascourret, M. P.: Les Anomalies des complexes ventriculaires electriques et leur importance pronostique dans les cours de l'insuffisance cardiaque, *Rev. de med.* 41: 587, 1924.
- (d) Pardee, H. E. B., and Master, A. M.: Electrocardiogram and Heart Muscle Disease, *J. A. M. A.* 80: 98 (Jan. 13), 1923.
2. Willius, F. A., and Killins, W. A.: The Occurrence and Significance of Electrocardiograms of Low Voltage, *Arch. Int. Med.* 40: 332, 1927.
3. Katz, L. N., and Kissin, M.: A Study of Lead IV, *AM. HEART J.* 8: 595, 1933.
4. Shipley, R. A., and Halloran, W. R.: The Four-Lead Electrocardiogram in 200 Normal Men and Women, *AM. HEART J.* 11: 325, 1936.
5. (Personal Observations of the Authors.)
6. Sprague, H. B., and White, P. D.: The Significance of the Electrocardiograms of Low Voltage, *J. Clin. Investigation* 13: 109, 1926.
7. Pardee, H. E. B.: The Clinical Aspects of the Electrocardiogram, New York, 1928, Paul Hoeber.
8. Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion. Further Observations on the Use of Chest Leads, *Arch. Int. Med.* 52: 752, 1933.
9. Standardization of Precordial Leads, *AM. HEART J.* 15: 107, 1938.
10. Oppenheimer, B. A., and Mann, H.: An Electrocardiographic Sign in Pericardial Effusion, *Proc. Soc. Exper. Biol. and Med.* 20: 421, 1923.
11. Eyster, J. A. E., Maresh, F., and Krasno, M. R.: The Nature of the Electrical Field Around the Heart, *Am. J. Physiol.* 106: 574, 1933.
12. Katz, L. N., Gutman, I., and Ocko, F. H.: Alterations in the Electrical Field Produced by Change in the Contacts of the Heart With the Body, *Am. J. Physiol.* 116: 302, 1936.
13. Katz, L. N., Sigman, E., Gutman, I., and Ocko, F. H.: The Effect of Good Electrical Conductors Introduced Near the Heart on the Electrocardiogram, *Am. J. Physiol.* 116: 343, 1936.
14. Katz, L. N. et al.: Concerning a New Concept of the Genesis of the Electrocardiogram, *AM. HEART J.* 13: 17, 1937.
15. Wilson, F. N.: The Distribution of the Potential Differences Produced by the Heart Beat Within the Body and at Its Surface, *AM. HEART J.* 5: 599, 1930.
16. Wolferth, C. C., and Wood, F. C.: The Prediction of the Amplitude and Direction of Waves in the Precordial Leads CR, CL, and CF on the Basis of the Limb Lead Findings, *AM. HEART J.* 20: 12, 1940.
17. Katz, L. N., and Korey, H.: Manner in Which Electric Currents Generated by the Heart Are Conducted Away, *Am. J. Physiol.* 111: 83, 1935.
18. Goodman, M.: Effect of Edema on the Amplitude of the Electrocardiographic Waves, *AM. HEART J.* 10: 269, 1934.

THE AORTIC VALVULAR LESION ASSOCIATED WITH THE AUSTIN FLINT MURMUR

BENJAMIN A. GOULEY, M.D.
PHILADELPHIA, PA.

ONE explanation of the mechanism of the Austin Flint murmur which is acceptable to many clinicians is that blood regurgitating through a damaged aortic valve strikes against the anterior mitral curtain and pushes it laterally into the auriculoventricular blood stream. Thus, a functional obstruction is created at the mitral valve. The anterior mitral leaflet, which is displaced from its usual mural position in diastole, now hangs suspended between two downflowing streams of blood and is impinged on by both, and this sets up the vibrations which cause the rumbling presystolic apical murmur of aortic regurgitation. This explanation is a summary of many views, all of which, although they differ more or less in detail, take into consideration the essential factor of aortic regurgitation and the likely secondary factor of functional mitral valvular obstruction.

A rather small minority of patients with aortic regurgitation have a Flint murmur; this fact was apparent to the early investigators, but was never fully accounted for. The above explanation of the mechanism of the murmur, like all others, therefore remains incomplete. It is likely that some anatomic or physiologic difference marks off those with the murmur from the majority of patients with aortic regurgitation. Until recently, detailed investigation of the changes in the aortic leaflets in such cases was seldom attempted; most pathologists were satisfied when they found that the mitral valve was normal in the presence of aortic regurgitation.

It has generally been thought that the Flint murmur is due to a lesion involving the posterior aortic leaflet. This assumption was largely based on theoretical considerations, until Herrmann produced aortic regurgitation in dogs by perforation and laceration of the posterior aortic leaflet. After the operation, many of these dogs (36 per cent) had a diastolic apical murmur and a diastolic apical thrill. Such signs did not appear in the few dogs whose right or left anterior aortic leaflets were damaged without injuring the posterior cusp. An experimental basis was thus established for the Flint murmur. This experimental lesion, however, is not identical with the lesions which we have constantly noted in patients who came to necropsy. The structural change to which we refer consists of two lesions, namely, (1) a peculiar deformity of the right anterior leaflet, and (2) a thickening

From the Laboratories of Pathology and Cardiology of the Philadelphia General Hospital, the Laboratory of the Jewish Hospital, the Laboratory of Pathology and the Robinette Foundation of the University of Pennsylvania.

Received for publication Nov. 2, 1940.

of the anterior (aortic) mitral curtain, especially of its lower portion, on the ventricular aspect, where the chordae tendineae are attached. The lesion of the right aortic leaflet is the more important; that of the anterior mitral curtain is secondary, and is the result of the constantly recurring impact of the regurgitant stream on that curtain.

The right aortic leaflet in ten cases, of which 5 will be discussed here, presented a concave, cup-shaped deficiency of its inner portion, i.e., the portion of the leaflet adjacent to commissure No. 2 (connecting the right anterior and the posterior aortic leaflets). This inner portion of the right aortic leaflet sagged, and the free margin pouched or drooped outward into the ventricular lumen. In one case the entire leaflet had weakened and was stretched, and its free margin was rolled and everted. In this instance, the inner corner of the leaflet was notably more seriously involved, and sagged to a lower level. In all cases this cup-shaped depression faced more or less laterally in the direction of the anterior mitral curtain. The other leaflets were either normal or involved in what often was a syphilitic process, that is, they were retracted in variable degree as is commonly the case in that type of valvulitis.

The second feature, namely, the thickening of the anterior mitral curtain on its ventricular aspect, was variable in its development. In some cases the lower half of the curtain, including the site of attachment of the chordae tendineae, showed an almost uniform increase in thickness and opacity (Fig. 1). In most instances, this was notable at the inner and usually the lower portion of the curtain, and the endocardial sclerosis also involved the mural endocardium of the adjacent ventricular septum. In one instance this thickening took on unusual aspects, giving rise to spindle-shaped and cylindrical enlargement of the chordae tendineae at the point of their attachment with the mitral curtain (Fig. 3). Possibly masses of fibrin had originally been deposited in these areas. In two cases, endocardial ridging down along the ventricular septum suggestively marked out a diagonal path leading from the damaged right aortic leaflet. Time is undoubtedly a factor in producing these endocardial changes on the anterior mitral curtain. They almost certainly are the result of friction, and it is likely that in some cases death ensues before marked changes occur.

Of the ten patients who presented this type of aortic valvular deformity, nine were men and all were between the ages of 30 and 45 years. The majority of these patients had syphilitic cardiovascular disease. In one case there was a complicating subacute bacterial mitral endocarditis, which we believe had no connection with the aortic valvular deformity, and in two the aortic lesion was due solely to rheumatic disease.

REPORT OF CASES

CASE 1.—J. S., a negro, aged 38 years, was admitted to the Philadelphia General Hospital on the medical service of Dr. W. E. Robertson, complaining of

paroxysmal dyspnea and edema of the legs. There was palpitation, but no precordial pain. Examination revealed basal pulmonary congestion, ascites, edema of the legs, and a blood pressure of 200/0. He had an aortic diastolic murmur which was transmitted down the left border of the sternum. In the apical area, in the fifth and sixth intercostal spaces, beyond the midclavicular line, there was a rumbling presystolic murmur, followed by a short systolic murmur. The heart was greatly enlarged to the left, the peripheral signs of aortic regurgitation were well developed, and the blood Wassermann and Kahn reactions were strongly positive. The clinical diagnosis was syphilitic cardiovascular disease, with aortic regurgitation and a Flint murmur.

Necropsy showed a heart weighing 850 grams, a markedly enlarged left ventricle, syphilitic aortitis, and slight widening of commissure No. 2. The right anterior leaflet extended out into the valvular lumen more than the others, which were slightly retracted, and it showed a distinct tendency to pouch and sag at its inner corner (Fig. 1). The free edge at this corner was thickened and dropped downward, forming a depressed cupping. No local sagging was noted in the other aortic leaflets. The anterior mitral leaflet showed definite thickening and an increased opacity of the lower portion on the ventricular aspect. The upper ends of the chordae tendineae were thickened at their points of attachment. However, the mitral valve, when viewed from its inner aspect, was entirely normal.



Fig. 1.—Case 1. The inner portion of the right anterior aortic leaflet pouches out into the ventricular lumen in the direction of the anterior mitral curtain. The free margin of this part of the leaflet was slightly rounded and lipped. The lower portion of the anterior mitral curtain was moderately and uniformly thickened, as were the chordae tendineae at their points of attachment. The mitral valve, viewed from its inner aspect, was normal.

CASE 2.—R. R., a negro, aged 30 years, was admitted March 29, 1934, to the Philadelphia General Hospital on the medical service of Dr. T. Schnabel, complaining of shortness of breath and swollen ankles. Cardiac failure had first been noticed in March, 1931, since which time the patient had suffered repeated attacks of dyspnea, and eventually developed orthopnea and dizziness. There was a history of syphilitic infection in 1920, for which the patient had received treatment for nine months.

Examination showed a young, well-nourished man, with a blood pressure of 200/50 in both arms, and with all the peripheral signs of aortic regurgitation. The heart was greatly enlarged; the left border was in the axilla in the fifth and sixth intercostal spaces. No thrills were palpable. The blood and spinal fluid Wassermann reactions were negative. Nevertheless, mild antisyphilitic treatment was administered. When the patient was readmitted to the hospital the serologic reactions were strongly positive (4 plus). Auricular fibrillation developed and resulted in fatal cerebral embolism on October 18, 1935.

Necropsy revealed a huge heart, weighing 980 grams; the left ventricle was markedly dilated. Aside from relative insufficiency, the mitral valve was normal, as were the tricuspid and pulmonic. There was no widening of the aortic commissures despite the presence of syphilitic aortitis. The aortic leaflets were slightly thickened; only the right aortic, however, showed a rolling of its free edge, in addition to which there was a sagging of the inner portion of the leaflet. On the ventricular aspect of the anterior mitral curtain there was a patchy, irregular thickening, with numerous, small, pinkish-gray elevations of the endocardial surface.

CASE 3.—A. G., a negro, aged 45 years, was admitted August 14, 1935, to the Philadelphia General Hospital on the medical service of Dr. Truman Schnabel, complaining of dyspnea which had begun eighteen months before as "asthma."

Examination revealed orthopnea, venous hypertension, and a flat percussion note and tubular breathing over the upper lobe of the right lung. The entire chest was filled with râles, and this precluded satisfactory examination of the heart. On one occasion a diastolic apical murmur was heard. The apical beat was in the sixth intercostal space in the anterior axillary line. The blood Wassermann reaction was strongly positive (4 plus). Death occurred suddenly on August 18.

Necropsy showed a greatly dilated, bowl-shaped left ventricle. There was a hinge valve deformity* of the right anterior aortic leaflet. The inner portion of this thickened leaflet showed an exaggerated sagging which formed a low, cup-shaped depression. The posterior and left anterior leaflets were entirely normal. The inner and lower aspect of the anterior mitral curtain (ventricular side) was thickened and ridged. The mitral valve itself was normal.

The aorta was the seat of a diffuse, syphilitic aortitis, and there was an aneurysm of the horizontal arch, involving the innominate artery.

Note: Although the diastolic apical murmur could not be clearly defined as an Austin Flint murmur, the post-mortem observations almost certainly identify it as such.

CASE 4.—P. M., a negro chauffeur, aged 39, was admitted to the Philadelphia General Hospital on the service of Dr. F. Kalteyer, October 19, 1939, complaining of chills and nosebleeds. Severe, sharp precordial pain had been experienced with increasing frequency, and shortness of breath and great weakness were noted one week before hospitalization. He had had a penile lesion at the age of 18.

Physical examination revealed a very anemic, but well-nourished man who was slightly dyspneic and had moderate clubbing of the fingers. The blood pressure was 120/58. A to-and-fro murmur was heard at the aortic area. Diastolic and systolic murmurs were heard in the fifth intercostal space, and replaced both heart sounds. The diastolic rumble increased in intensity up to the first sound, merging with it to form a long and almost continuous mitral murmur.

*"Hinge valve" is a term applied in the Philadelphia General Hospital to the strikingly everted right aortic leaflet that is often accompanied by high-pitched, musical, diastolic murmurs.¹ Such a murmur may have been obscured in this case by the noisy respiration.

Death occurred shortly after admission, before the serologic studies were completed.

Necropsy showed a heart weighing 450 grams, with a large left ventricle of globular shape which was more dilated than hypertrophied. The anterior mitral leaflet on its auricular aspect was covered in its upper portion (the free margin was not involved) by an ulcerating thrombotic mass (subacute bacterial endocarditis, *Streptococcus viridans*). Viewing the anterior mitral curtain on its ventricular aspect, it was noted that the ulcerative process had just about broken through the body of the leaflet. The upper portion of the curtain on this aspect showed some fibrinous deposit which extended up toward the base of the posterior aortic leaflet. The latter, however, was entirely normal.

The right anterior aortic leaflet sagged, especially its inner portion, which presented a cup-shaped deficiency (Fig. 2). The free edge was rolled and thickened. The posterior and the left anterior leaflets were normal, except possibly for a slight widening of the intervening commissure. There were marked thickening and opacity of the mural endocardium, extending from the weakened inner corner of the right aortic leaflet diagonally down and across the ventricular septum, and reaching the lowermost portion of the anterior mitral curtain, which, together



Fig. 2.—Case 4. The right anterior aortic leaflet shows marked sagging and cupping, especially its inner portion (A). The posterior leaflet is normal except for slight retraction at the commissure joining it with the left aortic leaflet, also despite the presence of fibrinous deposit reaching its base from the adjacent vegetative mitral endocarditis (B). Note marked sclerotic thickening (arrows) along lower portion of anterior mitral curtain and adjacent septal endocardium which is distinct from the acute fibrinous extension from the mitral lesion to the chordae tendineae. The sclerotic endocarditis is confined to a belt leading down diagonally from the damaged right aortic leaflet.

with its innermost chordae tendineae, shared in the sclerotic process. This sclerosis was evidently chronic, and independent of the ulcerative lesion high in the body of the anterior mitral curtain. It appeared to be sharply marked off, especially in its upper portion beneath the weakened right aortic leaflet, and thus suggestively outlined a track that was followed by the downflowing regurgitant blood stream.

Above commissure No. 2, and almost imperceptibly above commissure No. 3, there were small, slightly elevated, rather moist and translucent swellings of the intima of the aorta. Histologically, the aortic wall showed typical syphilitic changes in these areas.

Note: In this case of aortic regurgitation accompanied by a Flint murmur, the syphilitic aortic valvular disease was confined to the right aortic leaflet, giving rise to a characteristic deformity and a "directed" mural endocardial sclerosis marking the line of regurgitation. The posterior aortic leaflet was normal.

CASE 5.—A. H., aged 35 years, a white elevator operator, was admitted to the Philadelphia General Hospital March 23, 1940, on the service of Dr. P. Jump, complaining of shortness of breath. He had had rheumatic fever in 1935, but otherwise had been in good health until Christmas, 1939, when he became dyspneic, and soon thereafter he noted swelling of the ankles.

Examination revealed rheumatic heart disease. There was a marked presystolic murmur at the apex, followed by a short systolic murmur. This apparent mitral stenosis was accompanied by signs of aortic valvulitis, i.e., a short systolic and diastolic murmur were heard in the aortic area. The blood pressure was 140/70. Both lung bases were congested. Right-sided heart failure was evidenced by venous hypertension, an enlarged liver, and some edema of the legs. Fluoroscopic examination revealed a large left ventricle, a prominent pulmonary arterial salient, and hilar pulmonary congestion. The electrocardiogram showed prolongation of the P-R interval (.21 second) and notched P waves. Death was sudden on April 4, 1940.

Necropsy: Both ventricles were enlarged and hypertrophied, particularly the left.

There was, surprisingly, no mitral stenosis. The mitral valve was 12.5 cm. in circumference, so that there was apparently a relative insufficiency. There was very slight thickening at the free edge (Fig. 4); also, increased vascularity was noted at the base of the valve. The important changes were on the ventricular aspect of the anterior mitral curtain and in the right aortic leaflet. The latter exhibited a collapse fibrosis. The upper portion of the leaflet, including its free margin, had largely caved inward toward the aortic wall. Fibrous stiffening maintained this peculiar position. The median portion of the leaflet, leading to commissure No. 2, was most seriously involved; the upper line of the leaflet had practically disappeared, and was replaced by a marked concavity (Fig. 3). The other leaflets showed some thickening and were lightly fused to each other at the commissures, but they did not exhibit the collapse seen in the right anterior leaflet.

The lower portion of the anterior mitral curtain (ventricular aspect) showed a generally increased thickening and opacity, and, further up, the endocardial surface was ridged and irregularly roughened. Some of the more prominent ridges were almost horizontal, and their inner ends tipped upward in the direction of the membranous septum and the damaged right anterior leaflet.

The chordae tendineae were elongated, but, in addition, they showed, especially those streaming laterally, marked spindle-like thickening at the point of their insertion into the mitral curtain. These thickenings had a smooth surface and were all most prominent on the ventricular or aortic aspect of the curtain; in contrast, the mitral valve was practically normal in appearance when viewed from the auricular aspect.

DISCUSSION

Flint² thought that functional mitral stenosis was the cause of the murmur, and, since his time, many suggestions have been made as to how and when such a situation would develop. Guiteras³ stated that the mitral leaflets are not "floated upwards," as was suggested by



Fig. 3.—Case 5. Note marked deficiency and cupping of inner portion of right anterior aortic leaflet (A). Arrows mark sclerotic thickening and ridging of the anterior mitral curtain. Note spindle shape and bulbous thickening of the chordae tendineae at the points of insertion in the mitral leaflet. Posterior aortic leaflet is normal.

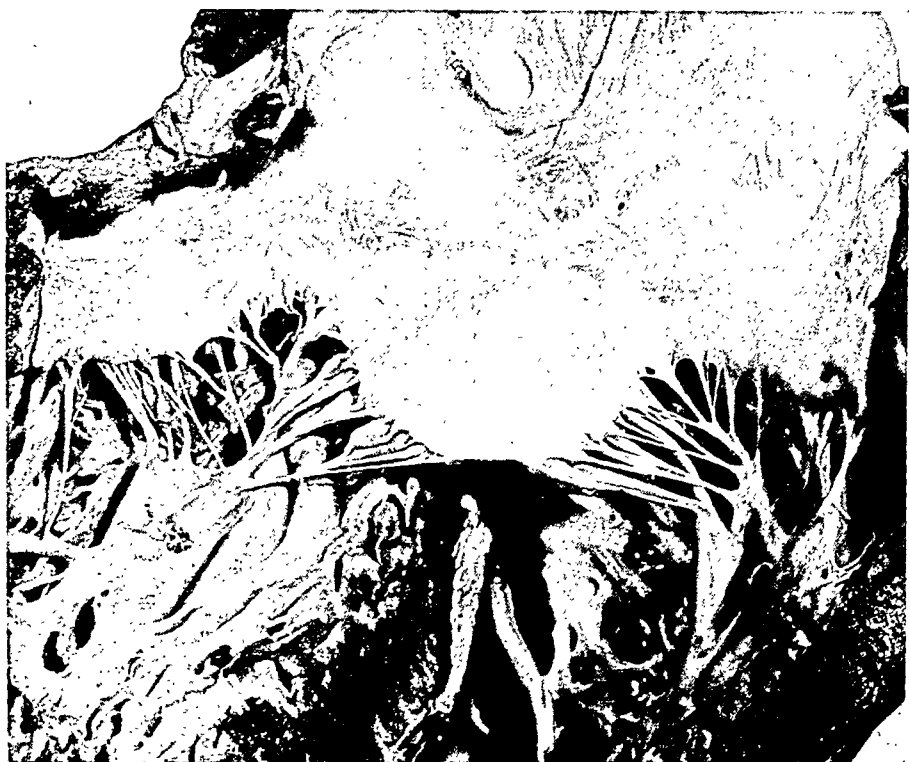


Fig. 4.—Case 5. The mitral valve is practically normal. There is slight thickening of the anterior mitral flap, and the bulbous thickening of the upper ends of the chordae tendineae which was so prominent on the ventricular aspect can barely be seen.

Flint, but are *actively driven* against the auricular blood flow by the "general arterial tension." Apparently he believed that the force striking against the mitral curtain, which diminished the valvular channel, did not derive directly from the regurgitant aortic stream, but was rather the result of the speedy filling of the ventricle from both the aorta and the auricle. J. C. Da Costa⁴ believed that dilatation of the left ventricle was an essential factor, and that this displaced the anterior mitral curtain, making it tense and the target of two oppositely directed streams of blood. In this connection, it may be pointed out that, in almost every case, predominant aortic regurgitation is accompanied by dilatation of the left ventricle, but the Flint murmur is not universally present. Broadbent⁵ said that the regurgitant aortic stream impinged on the anterior mitral curtain, causing it to vibrate; he appeared to be clearer on this point than his contemporaries, yet this also did not explain the *occasional* occurrence of the Flint murmur in aortic regurgitation. Finally, recent experimental work seems to indicate that the anterior mitral curtain is itself of little importance in the pathogenesis of the murmur; it acts merely as the transmitter of vibrations which are set up in the aortic leaflets.⁶

The importance of the associated aortic regurgitation has generally been recognized, but the relationship between the organic aortic lesion and the presumed functional mitral involvement has never been clear. The aortic valvular deformity herein described, the more or less well-developed changes on the ventricular aspect of the anterior mitral curtain, and the occasional tell-tale markings on the intervening ventricular septum constitute strong evidence, in our opinion, that the regurgitating blood is directed or "grooved" down and across the ventricular septum, forcing the anterior mitral curtain into the auriculoventricular current. We believe that this peculiar anatomic and physiologic variation of aortic regurgitation is in most instances the cause of the Flint murmur. If this is borne out by other observers, it will establish the validity of a functional mitral valvular stenosis.

The reason for the involvement of a precise part of a particular aortic leaflet (right anterior) is not clear. The constant location of this valvular defect in cases of varied etiologic origin suggests that a mechanical factor is of some importance. Possibly the point of maximum impact of the diastolic aortic recoil is, in some cases, at the inner corner of the right aortic leaflet; this point of greatest strain becomes evident when the valvular structure is undermined by inflammatory processes. Syphilitic valvulitis is common, whereas rheumatic or other infectious lesions are relatively uncommon. It appears that some destructive process incidental to infection, usually syphilitic, plays an important role. We have previously pointed out that the right anterior aortic leaflet was almost constantly involved in the "hinge-valve" lesion associated with musical diastolic murmurs, and that destruction of the supporting fibro-elastic "basket" of that leaflet by syphilis was a de-

termining factor in the subsequent valvular deformity.¹ It is probable that a similar inflammatory process is directed by some mechanical factor in the localization and development of the valvular deformity of the Flint murmur.

The role of posterior valve leaflet lesions.—The eccentric, cup-shaped depression of the right aortic leaflet occasionally occurs in the adjacent portion of the posterior leaflet as an associated lesion. We have not seen it there as the sole aortic valvular deficiency in cases featured by the Flint murmur. This is mentioned because the posterior leaflet is considered the site of lesions responsible for the murmur. It is conceivable that the murmur in some cases is caused by posterior leaflet changes which allow that leaflet to drag or flap, or in some way to hang out loosely in the lumen. In syphilitic aortic regurgitation, the most common type of heart disease with which the Flint murmur occurs, such lesions of the posterior leaflet are rare. Far more commonly this leaflet is shortened, thickened, and retracted toward the aortic wall, allowing free regurgitation and minimizing the possibility of abnormal vibration. In an occasional case of subacute bacterial endocarditis, ulceration and perforation at the base of the posterior aortic leaflet may provide a small aperture which allows diastolic leakage under pressure. This might well be a cause of marked vibration which would be easily transmissible to the anterior mitral curtain. We have not seen such a case,* and we believe that it is uncommon. It would constitute a clinical counterpart of the experimental lesion of Herrmann. We have not seen the left anterior aortic leaflet involved in this type of valvular deficiency. Regurgitation caused by a defect in this leaflet would scarcely touch the anterior mitral curtain with the heart tilted as it normally is in man.

It is interesting that, although syphilitic aortitis remains undoubtedly the chief cause of aortic valvular insufficiency in these cases, other types of heart disease are not excluded. This has been previously noted,⁸ although seldom supported by necropsy confirmation. In Case 5 (A. H.), the history clearly implicated rheumatic fever, and serologic tests for syphilis were negative. The presystolic apical murmur was regarded unhesitatingly as a manifestation of advanced mitral stenosis. The Flint murmur is rare in rheumatic heart disease because isolated aortic regurgitation is not often encountered, and also because even moderate stiffening of the anterior mitral curtain by rheumatic inflammation would lessen the chance of vibration. Nevertheless, aortic valve insufficiency does occur sometimes rather acutely in children and in young adults in the course of rheumatic fever, before mitral stiffening has developed, and in such patients a Flint murmur may occasionally be heard.

In attempting to correlate changes in the aortic leaflets with the Flint murmur, it must be realized that other cardiac murmurs also have

*Herrmann's second case was apparently of this type.⁶ Sansom⁷ mentioned a case of Guiteras' which was featured by a congenital aperture in the posterior leaflet.

their origin in aortic regurgitation, and that confusion may develop if their identification is either incomplete or, as is sometimes the case, difficult. The ordinary, blowing, diastolic murmur of aortic regurgitation which is often transmitted down along the sternum is also not uncommonly heard in the axilla, unaltered and apparently directly propagated. In this area, it has been described as Foster's murmur,⁹ or the "axillary diastolic murmur in aortic insufficiency."¹⁰ The Flint murmur is a presystolic rumble which practically merges with the first heart sound, and it is limited to a small area at the apex, whereas the directly propagated diastolic murmur is more often heard at a higher level, out in the axilla. They differ sufficiently in most instances to

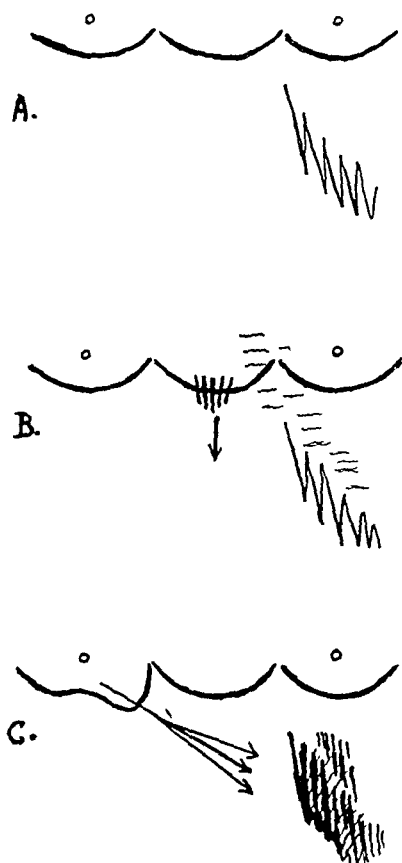


Fig. 5.—Schematic drawing showing (A) normal aortic valve and normal anterior mitral curtain; (B) perforation at the base of the posterior aortic leaflet, giving rise to vibrations (wave marks) in the aortic ring which are transmitted to the anterior mitral curtain as in the experimental aortic insufficiency of Herrmann. The anterior mitral curtain remains normal. (C) Sagging of the right anterior leaflet, especially inner corner (lesion of the Flint murmur), with grooving or diversion of regurgitant stream against the anterior mitral curtain, causing frictional sclerosis of the latter.

permit identification. They may be heard in the same patient.¹⁰ Differentiation of the Flint murmur from presystolic apical gallop rhythm is apparently more difficult. Some clinicians consider the Flint murmur as nothing more than a form of presystolic gallop due primarily to the existence of a large atonic left ventricle.^{11, 12} We regard such a hypothesis as singularly ill-founded.

SUMMARY

In a series of ten patients who had Flint murmurs incidental to aortic regurgitation, a characteristic deformity of the right aortic leaflet was found at necropsy. This consisted of a concave, cup-shaped deficiency of the inner portion of the leaflet, so situated as to divert or "groove" the regurgitating blood toward the lower portion of the anterior mitral curtain. The latter exhibited on its ventricular aspect a variable degree of endocardial thickening which was interpreted as a frictional sclerosis.

The posterior aortic leaflet was normal in some cases, and in others was involved in a manner which we believe was insignificant. We do not attempt, on the basis of this small series of patients, to exclude posterior leaflet lesions as occasional factors of importance. Our experience indicates, however, that they are uncommon.

The pathologic changes support the original belief of Austin Flint that a functional mitral stenosis, brought about by aortic regurgitation, is the cause of the presystolic apical murmur bearing his name.

The author is indebted to the medical and laboratory staffs of the Philadelphia General Hospital for the privilege of reporting these cases.

REFERENCES -

1. Bellet, S., Gouley, B. A., Nichols, C. F., and McMillan, T. M.: Loud Musical Diastolic Murmurs of Aortic Insufficiency, *AM. HEART J.* 18: 483, 1939.
2. Flint, A.: On Cardiac Murmurs, *Am. J. M. Sc.* 44: 29, 1862.
3. Guiteras, J.: (a) Three Cases of Acute Endocarditis; Evidences of Dynamic Mitral Stenosis, *Med. News* 47: 533, 1885.
(b) Direct Functional Murmurs, *Trans. Ass. Am. Physicians* 2: 37, 1887.
4. Da Costa, J. C.: *Physical Diagnosis*, Philadelphia, 1913, Ed. 1, p. 310, W. B. Saunders Co.
5. Broadbent, J. F. H.: *Heart Disease*, London, 1900, Ed. 3, p. 151, Bailliere, Tindall and Cox.
6. Herrmann, G. R.: The Austin Flint Phenomenon, *AM. HEART J.* 1: 671, 1926.
7. Sansom, A. E.: *Diseases of the Heart and Thoracic Aorta*, London, 1892, p. 381, Chas. Griffin and Co.
8. Easby, M. H.: *Med. and Surg. Yearbook*, Physicians Hospital, Plattsburgh, N. Y., 1: 90, 1929.
9. Foster, B.: *Clinical Medicine*, London, 1874, p. 121, J. and A. Churchill.
10. Cole, R., and Cecil, A. B.: The Axillary Diastolic Murmur in Aortic Insufficiency, *Johns Hopkins Hospital Bull.* 19: 353, 1908.
11. Pezzi, C.: The Pathogenesis of the Flint Murmur, *Arch. Mal. du coeur* 9: 290, 1916.
12. Cuatrecasas, J., and Duclos, F.: Contribution to the Mechanism of Flint's Murmur, *Rev. Med. de Barcelona* 17: 195, 1932.

PAROXYSMAL VENTRICULAR TACHYCARDIA

ITS FAVORABLE PROGNOSIS IN THE ABSENCE OF ACUTE CARDIAC DAMAGE, AND ITS TREATMENT WITH PARENTERALLY ADMINISTERED QUININE DIHYDROCHLORIDE

JOSEPH E. F. RISEMAN, M.D., AND HARRY LINENTHAL, M.D.
BOSTON, MASS.

PAROXYSMAL ventricular tachycardia is generally regarded as an ominous condition, largely because it occurs as a complication of acute myocardial infarction. The following case reports emphasize that even very severe attacks of ventricular tachycardia, when not associated with acute cardiac damage, may be followed by complete recovery. The purpose of this communication is also to emphasize the fact that quinidine is useful in this condition. In one of the cases, effective treatment by means of parenteral injections of quinine is illustrated.

REPORT OF CASES

CASE 1.—Mr. D. H., 60 years old, had, for a period of 20 years, noticed slight substernal oppression on exertion. A routine physical examination at the time this symptom began revealed an apical systolic murmur; an electrocardiogram seven years later showed prolonged QRS complexes, inverted T waves, and slightly depressed S-T segments in Leads II and III (Fig. 1A).

About twenty years after the onset of cardiac symptoms, the patient had attacks of dizziness, associated with palpitation and irregular heart action, which lasted a few seconds to several minutes. Physical examination was negative except for slight cardiac enlargement and a soft blowing systolic murmur at the apex. The blood pressure was 120/80. The electrocardiogram (Fig. 1B) was essentially the same as it had been thirteen years previously. The precordial lead showed a positive initial deflection of the QRS complex, with moderate depression of the S-T segment and a negative T wave. The morning after the electrocardiogram was taken, he suddenly experienced marked, irregular palpitation, severe substernal pain radiating down the left arm, dizziness, and faintness. His color was ashen, and he perspired profusely. Sedatives and large doses of quinidine were administered, after which he vomited repeatedly. This first attack lasted several hours. During the following week, while in bed, he experienced numerous similar, but milder, attacks, each initiated by extrasystoles, palpitation, and an increase in the pulse rate from 80 to 150. The heartbeat during some attacks was grossly irregular, with a marked pulse deficit; during other attacks the heartbeat was regular, with occasional accentuation of the first or second heart sounds. Carotid sinus pressure exerted no influence on the cardiac rate or rhythm. Electrocardiograms during the attacks showed periods of irregularity caused by premature beats of ventricular origin, or long periods of ventricular tachycardia (Fig. 1C). After the attacks subsided, the electrocardiograms showed only slight differences, as compared with the original tracing of thirteen years previously (Fig. 1D).

From the Medical Service and Medical Research Laboratories of the Beth Israel Hospital, and the Departments of Medicine of Harvard Medical School and Tufts Medical School, Boston, Massachusetts.

Presented before the New England Heart Association, January 29, 1940.

Received for publication Nov. 6, 1940.

When the ventricular rate rose above 150 the patient suffered severe substernal pressure, with pain radiating down the left arm. Quinidine in an amount sufficient to cause nausea and anorexia slowed the rate to 120 or 130 and relieved the pain. A maintenance dose of 3 grains every four hours was administered day and night. During the attacks of ventricular tachycardia 3 grains of quinidine every hour were required to maintain the lower ventricular rates. The largest amount administered in any one day was 42 grains. Constant medical supervision was required, and it is believed that myocardial damage was obviated in large measure by this regime.

These attacks of tachycardia decreased in frequency and severity, and disappeared entirely after seventeen days. Throughout a three-week period of observation he showed no evidence of myocardial infarction. The blood pressure remained at 120/80. There was never any elevation of temperature. The leucocyte count was 8,500. The corrected sedimentation index varied from 0.42 to 0.60. The electrocardiogram between and after attacks showed the original characteristics.

Subsequent Course.—In the four years which have elapsed since the above attack, the patient has had two additional attacks. One occurred eleven months later, while he was overexerting himself during a snowstorm, and lasted three hours, during which time he vomited frequently. The third attack, nine months later (Fig. 1F), lasted fifteen hours, during which time he received 6 grains of quinidine sulfate every two hours. Vomiting again made it difficult to ascertain how much of this quinidine was absorbed. In none of these attacks was there any change in electrocardiogram, blood cell count, or sedimentation rate to indicate cardiac damage, either as a cause or result of the ventricular tachycardia (Fig. 1G).

Since his last attack over two years ago, the patient has been taking 5 grains of quinidine sulfate twice daily. He has led an active, normal life, and does not have as much discomfort on walking as formerly.

COMMENT

The recent work of Blumgart, Schlesinger, and Davis¹ demonstrates that acute coronary occlusion may produce temporary anoxemia without myocardial infarction and with complete recovery if the collateral circulation is adequate. These authors have also shown that collateral circulation is formed as a response to the demands of the myocardium. It would seem likely, therefore, that the constant creation of such a demand by reasonable activity within the limits of the coronary circulation may be desirable to promote the formation of a collateral circulation. It is possible that the normal, active life of this patient during his twenty years of angina pectoris might have favored the formation of a coronary collateral circulation, and made him withstand the later attacks of ventricular tachycardia without any myocardial damage.

The difficulty in evaluating the effectiveness of quinidine sulfate in the presence of poor absorption from the gastrointestinal tract because of recurrent vomiting and circulatory collapse suggests the need of a soluble preparation of quinidine for parenteral administration. The following case illustrates again the inadequacy, at times, of the oral administration of quinidine sulfate, and indicates the value of intramuscular administration of quinine dihydrochloride under such conditions.

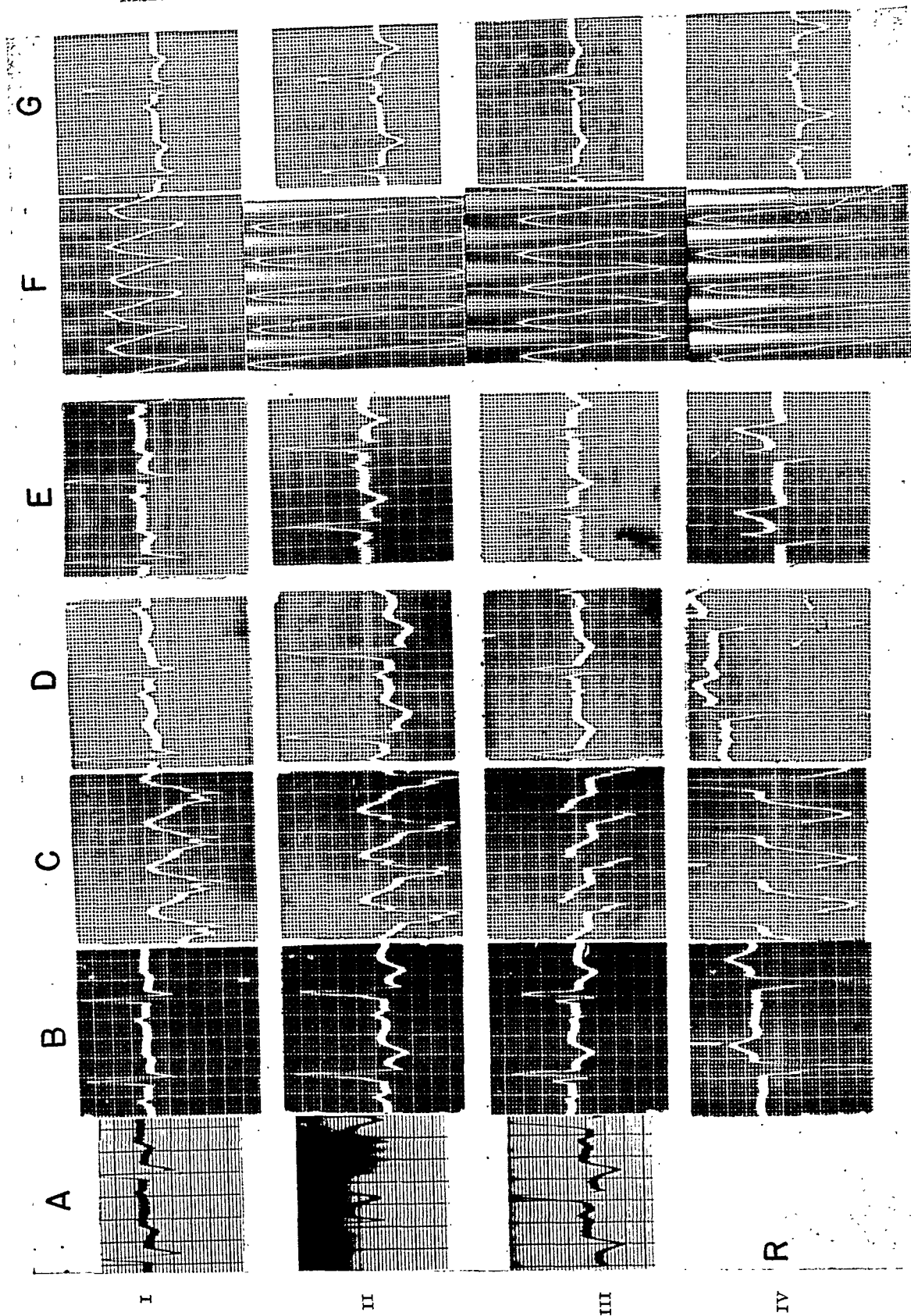


Fig. 1.—Electrocardiogram in Case 1 (D. H.): A, July 5, 1924, thirteen years before the first attack of ventricular tachycardia; B, Feb. 8, 1937, shortly after the onset of the first attacks of cardiac irregularity (Lead IV R, old method); C, Feb. 12, 1937, during an attack of ventricular tachycardia; D, Feb. 18, 1937, after recovery from repeated attacks of ventricular tachycardia; E, May 8, 1937, after two and one-half months of freedom from tachycardia; F, Sept. 2, 1938, during the third attack of ventricular tachycardia; G, Sept. 6, 1938, three days after cessation of the last attack (Lead IV R, new method).

CASE 2.—Mr. S. D., a German refugee, aged 54, was well until an attack of myocardial infarction in August, 1937. The attack was followed by transient aphasia, hemiplegia, and mesenteric embolism, and rest in bed for three months was required. The harrowing financial and nervous strain incident to establishing himself in this country prevented him from obtaining the physical and mental rest that his illness necessitated, but nevertheless he felt fairly well.

On Oct. 10, 1939, he suddenly felt faint, and noted that his heart was irregular. Physical examination showed nothing except frequent extrasystoles without compensatory pauses. The blood pressure was 140/80. The electrocardiogram (Fig. 2A) showed auricular extrasystoles, both singly and in groups, left-axis deviation, notched QRS waves in Leads III and IV, flat T waves in Leads I and II, and a negative, monophasic QRS in Lead IVR. Each premature auricular beat was followed by a prolongation of the P-R interval.

Quinidine sulfate, 5 grains four times a day, was prescribed. The patient remained in bed for three days, the arrhythmia and faintness subsided, and he felt perfectly well.

On Oct. 16, at 11:00 A.M., while shaving, he suddenly experienced rapid, regular beating of his heart, accompanied by a sense of weakness and faintness. When seen early in the afternoon, he was in bed and fairly comfortable except for the palpitation and slight substernal oppression. His expression was anxious, but he was mentally clear. There were definite pallor and moderate perspiration. The heart was not enlarged, the rhythm was normal, and the rate was 210, with no pulse deficit. The sounds were of good quality but not of uniform intensity, for at times either the first or second sound was accentuated. The blood pressure was 96/60. The lungs were normal, the liver was not enlarged, and there was no peripheral edema. Carotid sinus pressure did not influence the rate or rhythm. A diagnosis of ventricular tachycardia was made, and was confirmed by electrocardiogram (Fig. 2B). During the course of the examination he complained several times that everything became "dark," and that he felt as if he were "about to die." At these times the pulse could not be felt, the heart sounds were inaudible, and he became pale and lost consciousness for a few seconds.

Hospitalization was refused, and it was necessary to carry out treatment at home (Fig. 3). Approximately three hours after the onset of the attack, he was given $\frac{1}{8}$ grain of morphine sulfate hypodermically, followed by 10 grains of quinidine sulfate every hour for three doses. After the second dose of quinidine the patient vomited a large amount of undigested food, and it was obvious that the quinidine could not have passed through this mass into the intestine. The third dose of quinidine was vomited in tablet form. It was evident that the oral administration of drugs was of little value. About seven hours after the onset of the attack, therefore, quinine dihydrochloride, in a dose of $7\frac{1}{2}$ grains in 5 c.c. solution, was given intravenously. Approximately one minute later marked tinnitus occurred, followed suddenly by another period of unconsciousness. Within fifteen minutes the ventricular rate dropped temporarily to 155, but the electrocardiogram was unchanged. Further intravenous therapy seemed unsafe; accordingly, quinine dihydrochloride was given intramuscularly in a dose of $7\frac{1}{2}$ grains every hour for five hours.

During the second, third, and fourth days it was again possible to administer quinidine by mouth, despite occasional vomiting. During this period the patient was uncomfortable and weak, and râles appeared at the base of the right lung, but his general condition was satisfactory. It was obvious that quinidine induced cardiac slowing, but it could not be administered orally in doses sufficiently large to reduce the rate to normal. On the fourth day atropine sulfate was administered at two-hour intervals for three doses, beginning with $\frac{1}{150}$ of a grain and increasing each dose so that the third dose was $\frac{1}{50}$ of a grain; this was without any demonstrable effect.

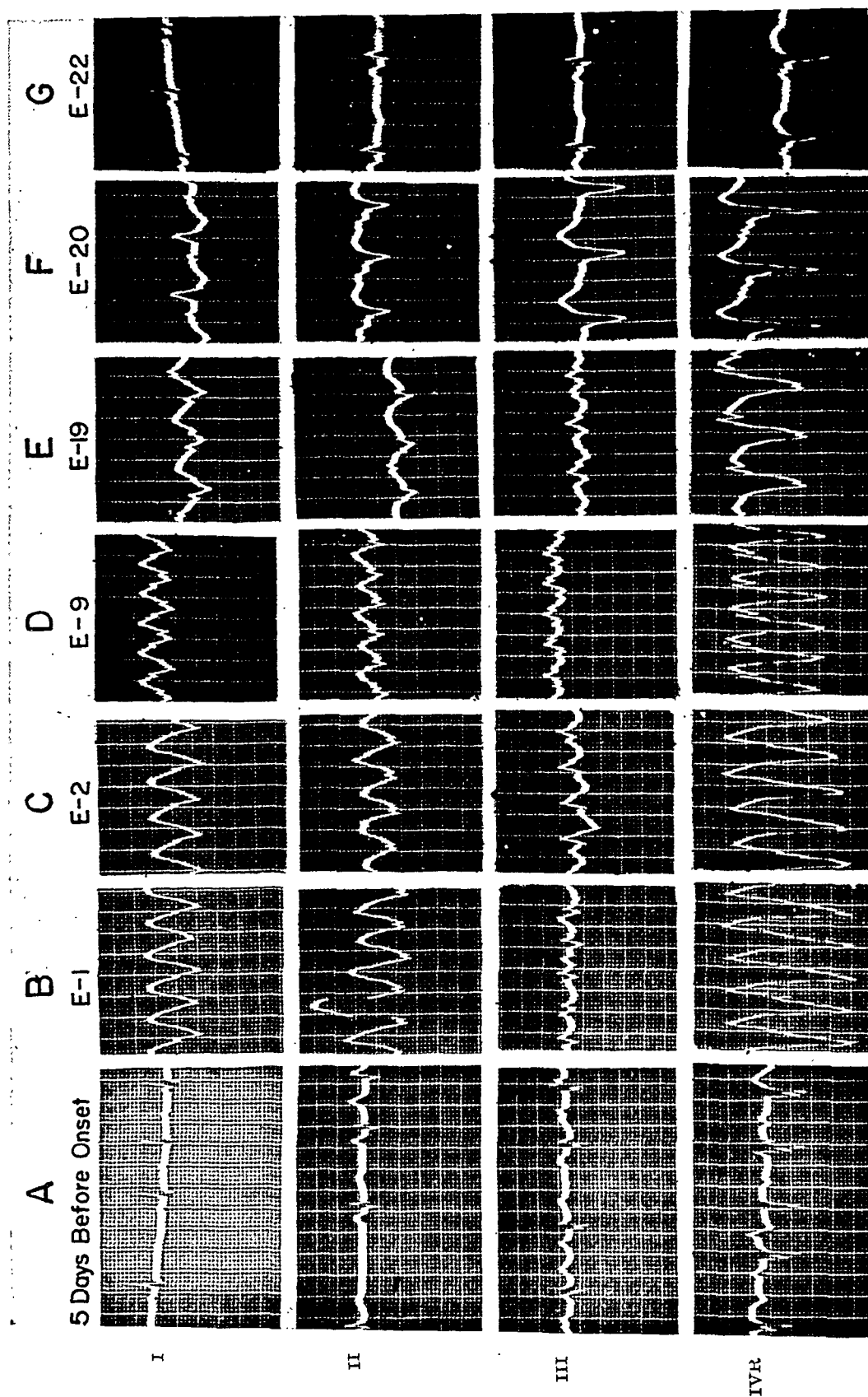


Fig. 2.—Electrocardiogram in Case 2 (S. D.): A, Oct. 11, 1939, shortly after the onset of auricular premature beats, five days before the onset of ventricular tachycardia; B, Oct. 16, 1939, approximately four hours after the onset of ventricular tachycardia; C, one-half hour after the administration of quinine dihydrochloride intravenously; D, Oct. 21, 1939, after the administration of 12 grains of digitalis; E, Oct. 24, 1939, shortly before the cessation of the attack; F, less than one hour after the cessation of the attack; G, Oct. 26, 1939, two days after the return to normal rhythm.

During the fifth day quinidine was discontinued because of vomiting. Six hours later his pulse rate began to rise. In ten hours it was again 210, and periods of unconsciousness occurred. The administration of quinidine sulfate was again followed by a fall in heart rate to 160, but the rhythm was not converted to normal. The patient's condition had become worse. There were signs of consolidation at the base of the right lung, and numerous râles at the base of the left. He developed respiratory difficulty, coughed frequently, and raised large amounts of sputum which was occasionally bloodstreaked. He had slight fever, and developed considerable abdominal distention and slight edema of his legs and over his sacrum. Cyanosis was controlled by oxygen therapy.

Digitalis was given in the hope of producing intraventricular block, and for its tonic effect on the failing myocardium. Because of the danger of precipitating ventricular fibrillation, the digitalis was given in doses of 3 grains every four hours, together with a maintenance dose of quinidine (5 grains), and frequent electrocardiograms were taken in order to recognize early any untoward digitalis effect. After the fourth dose of digitalis (on the sixth day), the heart rate again increased; the patient became weak and disoriented, complained of substernal pain, and had a period of unconsciousness during which the heart rate was over 200 and the pulse was imperceptible. The electrocardiogram (Fig. 2D) showed a definite decrease in the amplitude of the QRS complexes and a deep notch in Lead IV. Digitalis was discontinued and the dose of quinidine sulfate was again increased, after which the heart rate fell to 170 and the patient's condition improved slightly.

On the seventh day, despite quinidine, the heart rate increased and he had periods of unconsciousness. Quinine dihydrochloride was given intramuscularly again, and approximately one-half hour later his condition improved considerably. The intramuscular administration of quinine dihydrochloride was continued; at first it was given every hour when he was awake, and every 3 to 4 hours when he was asleep; later, every 2 hours, day and night. Each dose was followed by perceptible slowing of the heart.

On the ninth day it was evident that the auricular and ventricular rates were approximately the same, for after accentuation of the heart sounds for several consecutive beats the sounds would be normal in intensity. In the hope of speeding up the auricular rate and possibly decreasing the auriculoventricular block, atropine sulfate was given again in the same way that it had been on the fourth day. Again this had no demonstrable effect on the cardiac rate or rhythm; after the third dose, however, the patient became disoriented and confused. Because of weakness, seven doses of $\frac{1}{30}$ grain of strychnine sulfate were given at intervals of four hours.²

At 7:10 P.M. on the ninth day of the illness the heart rate was 124, and the electrocardiographic complexes were of the same character as had been observed previously, except that with the slowing of the rate the duration of the complexes increased (Fig. 1E). At 7:45 P.M. the heart rate was 108, the patient was sleeping comfortably, his pulse was full and strong, and his blood pressure was 120/80. The heart sounds were of good quality and of uniform intensity, and the rhythm was normal. The electrocardiogram (Fig. 2F) showed sinus rhythm, prolonged A-V conduction time (0.22 second), prolonged QRS complexes (0.12 second), deep S waves in Leads II and III, elevated S-T segments in Leads II, III, and IV, and inversion of the T wave in Lead I.

During the first three days after the termination of the tachycardia the patient was comfortable, but weak; the cough, abdominal distention, and edema disappeared, and the patient complained of his forced inactivity. Roentgenologic examination showed mottling of the lower two-thirds of both lungs, with a moderate degree of atelectasis and a small amount of fluid in the right pleural sac. The erythrocyte count was 4,710,000, the leucocyte count was 19,100, and the differential count was

normal. The urine examination was negative. The corrected sedimentation index was 0.72. The blood serologic reactions were negative. The patient remained in bed for two weeks, during which time his strength gradually returned. One month after his illness he resumed normal activity. The basal metabolic rate was minus 4 per cent. He has remained active during the two years which have elapsed since this attack.

This conversion of the rhythm to normal on the ninth day after the onset of the tachycardia took place approximately two hours after the last intramuscular injection of quinine dihydrochloride. A total of 240 grains had been given intramuscularly in the forty-eight hours preceding the conversion to normal rhythm. A maintenance dose of 5 grains of quinine was given intramuscularly four times a day for a few days, and then he was given quinidine sulfate by mouth (5 grains every four hours). The tinnitus disappeared forty-eight hours after the cessation of the massive doses of quinine dihydrochloride; the only untoward effect of the drug thereafter was moderate soreness and induration of the buttocks at the points of intramuscular injections.

DISCUSSION

That paroxysmal ventricular tachycardia may occur in persons without organic heart disease is not generally recognized, although several instances have been reported.³⁻⁶ The two patients presented here had coronary artery disease, but the tachycardia was not precipitated by any evident acute cardiac lesion. Recovery was complete. The duration of the attack in Case 2 was 8½ days. Although attacks of longer duration have been reported,⁷ most patients die earlier of cardiac insufficiency unless the paroxysm is ended or the ventricular rate is decreased.

Oppolzer,⁸ in 1866, advised small doses of quinine (1 to 2 grains every 2 to 3 hours) for its tonic effect in cases of tachycardia accompanied by a weak pulse. According to available knowledge, quinine and its isomer, quinidine, act on the heart by prolonging the refractory period and the conduction time. The latter effect results in a prolongation of the interval from the beginning of the Q to the end of the T wave (the duration of electrical systole⁹), as demonstrated by the electrocardiograms in Case 2. Frey, in 1918,¹⁰ found that quinidine hydrochloride was more effective than quinine in the treatment of auricular fibrillation. Lewis and his co-workers¹¹ later estimated that quinidine was five to ten times more effective than quinine in slowing the auricular rate; these authors concluded that all of the alkaloidal salts were of equal value because they were transformed in the stomach to the hydrochloride. It is obvious from the above cases, however, that when the attack is associated with circulatory collapse and vomiting (which frequently occur in acute arrhythmias) absorption from the gastrointestinal tract cannot be depended upon, and under such conditions of emergency an injectable preparation is desirable.

Hepburn and Ryckert¹² have advised the intravenous administration of quinidine sulfate. Since approximately 10 c.c. of saline are required to dissolve one grain of the drug, this method necessitates the intravenous administration of comparatively large volumes of fluid to cardiac

patients. It is impractical for the physician to carry such large volumes for emergency therapy, and, furthermore, the preparation of this solution requires more time than is usually available in such an emergency. The need of a small ampoule for emergency use is obvious. The preparations now available from the American pharmaceutical houses are relatively insoluble, but the more soluble quinine salts may be employed for parenteral use.

The indications for quinine therapy would appear to be: (1) acute arrhythmias or tachycardias, when quinidine would ordinarily be used but cannot be given by mouth because of vomiting or shock; (2) prolonged arrhythmias which are only partially controlled by the oral administration of quinidine sulfate.

The amount of medication necessary to interrupt the abnormal rhythm varies in different persons. In our experience with paroxysmal ventricular tachycardia, the administration of a small test dose is unnecessary, for it results in loss of valuable time, and the danger of collapse or death from continuation of the arrhythmia may be greater than the danger from hypersensitivity to the drug. An initial dose of 10 to 15 grains may be given, and this may be repeated every two, or two and a half, hours. This results in a gradual increase in effect, and, at the same time, permits evaluation of the effect of previous doses before continuing medication. More frequent administration may result in toxic effects after the therapeutic result has been obtained; less frequent administration (every four hours) is impractical because it is too time-consuming and does not result in an increased effect unless the amount given is increased with each dose.

Intramuscular administration is the route of choice. According to available knowledge,¹³ the drug is fixed by tissues, including the myocardium, within one-half hour. Renal excretion begins in about one-half hour and becomes minimal in approximately four hours. The effect on the auricular rate begins about one-half hour after oral administration, reaches a maximum in two hours, begins to decrease gradually after three hours, and has ceased almost entirely within twenty-four hours.¹¹

Levine¹⁴ has suggested the use of atropine in cases of ventricular tachycardia in which the attack is not controlled by quinidine orally. Carter and Traut² have reported that strychnine enhances the effect of quinidine. Neither atropine nor strychnine had any demonstrable beneficial effect in our case.

Levy¹⁵ has listed the untoward effects of quinidine, the majority of which were observed when auricular fibrillation had been converted to normal rhythm. In our experience with over 100 patients with coronary artery disease and normal rhythm (angina pectoris) who received 5 grains of quinidine sulfate four times daily, the only untoward effects observed were diarrhea and, in an occasional instance, urticaria or

slight gastric distress. The increase in ventricular rate which reputedly follows the administration of quinidine was not the rule, and, if it occurred, amounted to less than 10 beats per minute,^{16, 17} with these doses.

The possibility of inducing ventricular tachycardia or fibrillation by the administration of quinidine deserves special mention. The literature reports seven instances in which this apparently took place;^{15, 18, 19, 20} all except two occurred in cases in which quinidine was being given to abolish auricular fibrillation. In cases of auricular fibrillation the administration of quinidine is followed by a slowing of the auricular rate and an increase in the ventricular rate. Unless digitalis is given simultaneously with the quinidine, the absence of A-V block may result in a response of the ventricle to each auricular stimulus, and, therefore, ventricular tachycardia or fibrillation. In the two cases reported by Schwartz and Jezer,²⁰ the patients did not have auricular fibrillation, but suffered from frequent attacks of ventricular fibrillation which occurred spontaneously or could be precipitated by several drugs, including quinidine given intravenously. In treating patients with angina pectoris, we have not observed ventricular premature beats or abnormal rhythms as a result of quinidine therapy; indeed, the drug is frequently of value in eliminating premature contractions of the ventricle or auricle.

Prompt treatment of ventricular tachycardia requires prompt diagnosis. Although the electrocardiogram is the most specific diagnostic procedure, Levine and Fulton²¹ have pointed out the characteristics which make a clinical diagnosis possible: "First, the rhythm is rapid and essentially regular, but slight irregularities can be detected. Second, the quality of the first heart sound varies in intensity in some of the cycles. Third, attempts at vagal or ocular pressure prove ineffective in slowing the tachycardia." In our experience, the variation in the intensity of the heart sounds is the greatest aid in diagnosis. The lack of response to carotid sinus pressure serves to differentiate tachycardias originating in the ventricles from those originating above the A-V node. We were unable to recognize any irregularity in our two cases, either clinically or with the electrocardiogram.

SUMMARY

Two cases of paroxysmal ventricular tachycardia which demonstrate that this condition may occur without preceding or subsequent cardiac damage are presented. Under such conditions prompt diagnosis and treatment are essential, and may result in complete functional recovery. The importance of quinidine sulfate in the treatment is illustrated: even when the drug fails to cause conversion to normal rhythm, it may control the ventricular rate and thus prevent prolonged, severe, myocardial anoxemia, cardiac pain, and myocardial damage. In the presence of vomiting or circulatory collapse, poor absorption from the gastro-

intestinal tract makes parenteral therapy advisable; quinine dihydrochloride may be used under such conditions.

We wish to express our appreciation to Dr. Herrman L. Blumgart and Dr. Paul D. White, who saw these patients in consultation, and to the Misses Loretta and Rose Gilmartin for their excellent nursing care of patient S. D. under trying conditions.

REFERENCES

1. Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Studies of the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis, and Myocardial Infarction to the Pathologic Findings, *AM. HEART J.* 19: 1, 1940.
2. Carter, J. B., and Traut, E. F.: Quinidine and Strychnine in the Treatment of Premature Contractions, *Am. J. M. Sc.* 189: 206, 1935.
3. Andersen, M. C.: Paroxysmal Ventricular Tachycardia, *Am. J. M. Sc.* 181: 309, 1931.
4. Scott, R. W.: Observations on a Case of Ventricular Tachycardia With Retrograde Conduction, *Heart* 9: 297, 1922.
5. Strauss, M. B.: Paroxysmal Ventricular Tachycardia, *Am. J. M. Sc.* 179: 337, 1930.
6. Wilson, F. H., Wishart, S. W., Macleod, A. G., and Barker, P. S.: A Clinical Type of Paroxysmal Tachycardia of Ventricular Origin in Which Paroxysms Are Induced by Exertion, *AM. HEART J.* 8: 155, 1932.
7. Willins, F. A.: Paroxysmal Tachycardia of Ventricular Origin, *Boston M. and S. J.* 178: 40, 1918.
8. Oppolzer: Vorlesungen über die Krankheiten des Herzens und der Gefäße, edited by E. R. von Stoffella. Erlangen, 1866.
9. Landau, N.: Über die Verlängerung der Systole bei Tetanie und ihre Beeinflussung durch verschiedene Pharmaca, *Klin. Wchnschr.* 17: 93, 1938.
10. Frey, W.: Ueber Vorhofflimmern beim Menschen und seine Beseitigung durch Chinidin, *Berlin klin. Wchnschr.* 55: 450, 1918.
11. Lewis, T., Drury, A. N., Wedd, A. M., and Ilescu, C. C.: Observations Upon the Action of Certain Drugs Upon Fibrillation of the Auricles, *Heart* 9: 207, 1922.
12. Hepburn, J., and Rykert, H.: The Use of Quinidine Sulfate Intravenously in Ventricular Tachycardia, *AM. HEART J.* 14: 620, 1937.
13. Weisman, S. A.: Further Studies in the Use of Quinidine in the Treatment of Cardiac Irregularities, *Minnesota Med.* 22: 385, 1939.
14. Levine, S. A.: *Clinical Heart Disease*, Philadelphia, 1940, W. B. Saunders.
15. Levy, R. L.: The Clinical Toxicology of Quinidine, *J. A. M. A.* 78: 1919, 1922.
16. Riseman, J. E. F., and Brown, M. G.: Medicinal Treatment of Angina Pectoris, *Arch. Int. Med.* 60: 100, 1937.
17. Freedberg, A. S., Riseman, J. E. F., and Spiegl, E. D.: Objective Evidence of the Efficacy of Medicinal Therapy in Angina Pectoris. *AM. HEART J.* In press.
18. Davis, D., and Sprague, H. B.: Ventricular Fibrillation: Its Relation to Heart Block, *AM. HEART J.* 4: 559, 1929.
19. Kerr, W. J., and Bender, W. L.: Paroxysmal Ventricular Fibrillation With Cardiac Recovery in a Case of Auricular Fibrillation and Complete Heart Block While Under Quinidine Sulfate Therapy, *Heart* 9: 269, 1922.
20. Schwartz, S. P., and Jezer, A.: The Action of Quinine and Quinidine on Patients With Transient Ventricular Fibrillation, *AM. HEART J.* 9: 792, 1934.
21. Levine, S. A., and Fulton, M. N.: The Effect of Quinidine Sulphate on Ventricular Tachycardia, *J. A. M. A.* 92: 1162, 1929.

A QUANTITATIVE ELECTROCARDIOGRAPHIC STUDY OF DIGITALIZATION

ARTHUR J. GEIGER, M.D., LOREN F. BLANEY, M.D., AND
WILLIAM H. DRUCKEMILLER, M.D.
NEW HAVEN, CONN.

THERE appears to be a widespread impression that the electrocardiogram offers a method for quantitative estimation of the degree to which a patient is digitalized, and that such a record is a valuable aid in therapy. General statements to this effect are often made or implied in textbook discussions of digitals and the electrocardiogram. We have always felt reluctant to place such reliance on electrocardiographic features. It is, of course, acknowledged that a tracing may show certain changes in the RS-T segment and T wave which are so commonly associated with the administration of digitalis that the experienced observer immediately recognizes the abnormality as a characteristic effect of the drug. Moreover, the electrocardiogram may admittedly give valuable and sometimes almost certain evidence of *toxic digitalis action*. Our purpose, however, was primarily to learn whether any reasonably reliable and useful *quantitative* relationships exists with respect to electrocardiographic changes accompanying the *clinical* use of the drug in *therapeutic* doses.

A search of the literature has disclosed relatively few clinical studies bearing directly on this subject. One of the earliest electrocardiographic studies of digitalization in man was reported in 1915 by Cohn, Fraser, and Jamieson.¹ These observers clearly established that digitalis either lowered or inverted the T wave and depressed the RS-T segment in the majority of the tracings of the thirty-four patients whom they studied. Although some of the subjects were admittedly intoxicated by the doses of digitalis which were administered, nevertheless definite electrocardiographic changes apparently resulted from exhibition of the drug in therapeutic amounts, also. No attempt was made in this work to correlate the nature or extent of the changes in RS-T and T with degrees of clinical digitalization. Shortly after the report by Cohn and his collaborators, White and Sattler² described lowering of the T wave as an early effect of digitalis, and Pardee³ attempted to apply this phenomenon in the assay of digitalis preparations, but a lack of uniformity in the electrocardiographic effects of the drug was evident, even though the number of cases was small.

From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

Received for publication Nov. 9, 1940.

Larsen, Neukirch, and Nielsen⁴ reviewed the literature of this subject up to 1937, and described their own studies of the electrocardiographic changes which occurred in 15 normal adults after digitalis administration. As the subject has changed but little since then, a summary of their review may serve to indicate the present status of the problem. The consensus was that the P-R (or P-Q) intervals showed inconstant increases in duration, sometimes to the point of partial A-V block; but these changes could not be correlated with definite therapeutic states of digitalization. Only infrequent and relatively slight changes in the RS-T segment were observed, and these consisted usually of slight depression of the RS-T segment, or slight diminution in the height of the T wave. Concerning the T wave, Larsen and his associates commented, "Although the statements in the literature concerning the effect of digitalis administration on the shape of the T wave in normal subjects on the whole are in good agreement, all possible variations have been reported."

Stewart and Watson,⁵ in a recent study directed particularly toward the effect of digitalis on the form of the chest-lead electrocardiogram, illustrated eight representative types of electrocardiographic changes following digitalis. In only one of the series of tracings depicted (Stewart and Watson's figure 5), was either the RS-T segment notably depressed or the direction of T reversed in the conventional limb leads; on the other hand, a variable diminution in the amplitude of the T wave was noted in one or more leads of the other series of tracings shown. More recently, Levy and Boas,⁶ in comparing the electrocardiographic effects of gitalin and digitalis in thirty-five cases, stated that the two drugs gave similar results. In 11 cases neither drug in therapeutic doses produced changes in the T wave, whereas both drugs produced only slight alterations in T in twelve cases, moderate changes in ten, and marked effects in only two.

Although there is general uniformity of opinion that digitalis tends chiefly to depress the RS-T segment and diminish the amplitude of, or invert, the T wave, no direct correlation has apparently been established between the doses of digitalis which were administered and the resultant changes in RS-T and T, and there appears to be no reliable evidence from previous experimental work that the electrocardiogram can serve as a measure of the degree of digitalization of a patient.

The few reported studies of the Q-T duration all agree that digitalis effects a relative shortening of this interval. Cheer and Dieuaide⁷ considered that such a shortening of the Q-T interval was a more sensitive indicator of digitalis effect than lengthening of P-R, and a more definite change than alterations in the T wave.

Inasmuch as most of the leading reports concerning digitalis effects on the electrocardiogram antedated the general use of precordial leads, there has been relatively little written about this particular aspect

since the report by Strauss and Katz⁸ that digitalis may cause inversion of the T wave in the chest lead. In a thorough study of the subject in thirty cases, Stewart and Watson⁵ found that digitalis in therapeutic amounts resulted in some alteration of the T wave (which became lower in amplitude or reversed in direction) in all but one instance; changes in the RS-T segment were encountered in only a third of the cases, and were considered less marked than changes in the T wave. No attempt was made to relate the nature or degree of RS-T and T-wave changes to specific amounts of digitalis, and no correlation seemed evident, for various degrees of change, from none to considerable, were encountered in different cases in which similar amounts of digitalis were given. Casual observation of electrocardiograms taken routinely in this laboratory has abundantly demonstrated that digitalis may alter the RS-T segment level and T wave in the precordial lead, and has also confirmed the observation of Stewart and Watson⁵ that the degree of change suffered by T in the precordial lead is frequently more pronounced than in the limb leads.

It appeared, from these various reports, at least, that no definite quantitative relationship had been clearly established between digitalis concentrations and electrocardiographic changes. However, it seemed to us that the subject had been inadequately explored, and that further study was required, not only of the effects on normal subjects, but more particularly on patients with heart disease in various functional states. Moreover, it seemed promising to study more thoroughly the shortening of the Q-T interval which was attributed to digitalis by Cheer and Dieuaide;⁷ and, finally, it was considered interesting to learn whether precordial leads offer any advantage over the conventional limb leads in the quantitative estimation of digitalization.

SECTION I

A STUDY OF PROGRESSIVE DIGITALIZATION IN TEN NORMAL SUBJECTS

Ten normal male volunteers, ranging in age from 22 to 32 years, were studied electrocardiographically during progressive digitalization. None of the subjects had a history or physical signs of heart disease; roentgenograms of the chest showed hearts of normal configuration and size, and all had normal blood pressures.

Consistency in procedure was sought by administering the digitalis in a predetermined and uniform manner. Each subject received a total dose of digitalis, U.S.P. (Davies, Rose, and Company), which was calculated on the basis of 0.1 Gm. per 10 pounds of body weight, *plus* 0.15 Gm. for each day of the digitalizing period to compensate adequately for excretion. Since the digitalis employed met the U.S.P. XI assay requirements, the total quantity of the drug administered was approximately 30 per cent *in excess* of the theoretically optimal digitalizing dose.⁹ One-third of the total dose was given on the initial day, and the remaining two-thirds was administered in equal portions during the following four days.

Electrocardiograms, including the three conventional limb leads and precordial lead IV F,¹⁰ were recorded four hours after each dose, and several follow-up tracings were obtained at weekly intervals for one month longer, or until the electrocardio-

gram was identical with the original record. Electrocardiographic measurements included the P-R interval, Q-T duration (considered in relation to R-R time), changes in the RS-T segment, and alterations in the amplitude and direction of the T wave. Although these features were studied in all leads, it was found that Lead II was fully representative of the limb leads with regard to the P-R and Q-T measurements, and therefore, for reasons of simplicity, these particular data are presented in Table I for Leads II and IV F only. The T-wave amplitude and direction (see Table II) were studied in all four leads. The values indicated in Tables I and II represent average measurements of at least three successive complexes or waves.

TABLE I
ELECTROCARDIOGRAPHIC CHANGES FOLLOWING DIGITALIZATION OF NORMAL ADULT MALES

PATIENT NO.	DIGITALIS PER CENT	LEAD II				LEAD IV F			
		P-R SEC.	Q-T* SEC.	R-R* SEC.	"K"	P-R SEC.	Q-T SEC.	R-R SEC.	"K"
1	0	.18	.386	.766	.411	.16	.360	.733	.421
	130	.20	.333	.933	.346	?	.337	.960	.345
2	0	.17	.340	.713	.403	.16	.346	.740	.403
	130	.16	.380	1.233	.343	.17	.366	1.153	.342
3	0	.16	.393	.980	.397	?	.400	1.007	.394
	130	.18	.340	1.160	.317	?	.367	1.253	.327
4	0	.18	.373	.993	.373	.16	.380	.993	.382
	130	.17	.366	1.033	.365	.16	.353	.926	.367
5	0	.16	.375	1.000	.375	?	.376	1.060	.369
	130	.16	.340	.750	.393	.16	.326	.800	.365
6	0	.16	.360	.833	.394	.16	.420	.926	.436
	130	.16	.346	.713	.410	?	.393	1.000	.393
7	0	.14	.340	.700	.408	.16	.340	.680	.412
	130	.18	.360	.920	.376	.18	.346	.913	.363
8	0	.17	.393	.753	.454	.16	.360	.820	.397
	130	.18	.360	.726	.423	.18	.353	.753	.403
9	0	.16	.373	.806	.416	.14	.360	.800	.403
	130	.15	.360	.860	.388	.15	.353	.820	.386
10	0	.18	.367	.780	.415	.14	.327	.840	.357
	130	.20	.393	1.060	.381	?	.330	1.033	.320

*Values represent averages of 3 to 5 measurements.

RESULTS

As may be seen from Table I, the P-R duration increased not more than 0.02 second in about half the records, whereas the remainder showed no change or very slight shortening. These alterations were probably within the limits of expected variation for the changes in heart rate. The P wave was usually either absent or poorly defined in Lead IV F, and P-R intervals were not satisfactorily measurable. It was apparent that a change in the P-R duration could not serve as a quantitative measure of digitalization, even when moderately excessive doses of the drug had been administered.

2. The Q-T time was considered in relation to the cardiac cycle length, following the method of Cheer and Dieuaide,⁷ who employed a modification of Bazett's formula, as follows:

$$Q-T = \text{"K"} \text{ times the square root of R-R;}$$

or

$$\text{"K"} = Q-T \text{ divided by the square root of R-R.}$$

"K" has been found to be relatively constant within narrow limits when the heart is normal,¹¹ and increased when it is failing.⁷ It is evident from the equations that a decrease in Q-T, relative to R-R, will result in a smaller value for "K." Although Table I indicates that "K" was diminished in eight of the ten subjects at the height of digitalization, careful analysis of the intermediate electrocardiograms revealed that this change was not a progressive one; in fact, the values for "K" in the successive records of the majority of the subjects showed considerable irregular variation, and the seemingly consistent effects in Table I are probably quite fortuitous.

3. In a majority (60 per cent) of the normal records the RS-T segment was very slightly (less than one millimeter) above the isoelectric line, and was lowered to the isoelectric line during the administration of digitalis. In about half the records the RS-T segment was less than one millimeter below the isoelectric line at the height of the digitalis effect. These changes were not only regarded as within the limits of normal variation, but they were entirely too slight to serve as a quantitative measure of digitalization.

4. The T-wave changes during progressive digitalization were remarkable chiefly for their inconsistency in character and their relatively small magnitude. As may be seen from Table II, slight inversion of T developed only three times among the forty leads from the ten subjects, and T became diphasic only three times. A reduction in the amplitude of T was a common accompaniment of digitalization, and this was most pronounced in the precordial lead. But in only three of the subjects (Nos. 2, 8, and 10) was this a uniformly progressive effect with increasing digitalization; in all the remainder the T wave gained positive amplitude in one or more leads at either the theoretically optimal level of digitalization, as compared with the normal, or at the overdigitalization level, as compared with the optimal (note especially subject No. 4 in Table II). This result came as a distinct surprise. One is led to surmise that physiologic variations, as well as digitalis influence, must account for such alterations in the character of the T wave.

The indefinite effects of digitalis on the RS-T segments and T waves in each lead of the records from the normal subjects are graphically depicted in Figs. 2 and 3.

It is apparent from the above that the electrocardiographic changes which accompanied progressive digitalization of these normal subjects

TABLE II
T-WAVE CHANGES FOLLOWING DIGITALIZATION OF NORMAL ADULT MALES

PATIENT NO.	DIGITALIS PER CENT	T WAVES (MM.)			
		I*	II	III	IV F
1	0	+2.0	+4.0	+2.5	+4.5
	100	+2.5	+4.0	+1.5	+5.0
	130	+2.5	+2.5	±1.5	+5.5
2	0	+2.0	+2.5	±0.5	+4.5
	100	+1.0	+1.5	+0.5	+1.0
	130	+1.0	+1.0	+0.5	+1.5
3	0	+3.0	+7.0	+3.5	+7.0
	100	+1.5	+3.5	+3.0	+5.0
	130	+1.5	+6.5	+3.0	+6.0
4	0	+3.5	+4.5	+1.0	+8.0
	100	+1.5	+2.0	-1.0	+2.0
	130	+5.0	+4.5	±1.5	+5.0
5	0	+5.0	+4.5	-1.0	+6.5
	100	+2.5	+2.5	±1.0	±1.5
	130	+2.5	+2.5	±1.0	+4.0
6	0	+3.0	+3.0	+1.5	+5.0
	100	+2.0	+2.0	±1.0	+1.0
	130	+2.0	+2.0	0.0	+2.5
7	0	+2.0	+4.0	+2.5	+6.0
	100	+2.0	+2.5	+1.0	+3.0
	130	+2.0	+3.0	+1.0	+1.5
8	0	+3.0	+6.0	+3.5	+9.0
	100	+3.0	+4.0	+1.5	+6.0
	130	+3.0	+4.0	+1.5	+6.0
9	0	+2.0	+2.0	+0.5	+3.5
	100	+3.0	+2.0	-1.0	+6.0
	130	+1.5	+1.5	±0.5	+2.5
10	0	+3.0	+3.5	+0.5	+3.0
	100	+2.0	+1.5	-1.0	+2.0
	130	+1.0	+1.5	±1.0	+1.5

*Numerals refer to leads.

were too small in degree and too inconstant in character to indicate any quantitative correlation between the electrocardiographic effects and corresponding degrees of digitalization. This was true even when digitalis was administered in a dose which was presumably in the early toxic range.

SECTION II

A STUDY OF PROGRESSIVE DIGITALIZATION OF TEN PATIENTS WITH HEART DISEASE AND CONGESTIVE FAILURE

The possibility that patients with diseased hearts might show digitalis effects different in kind and in degree from those observed in the preceding experiments on normal subjects led us to study in similar fashion ten patients with congestive failure caused by heart disease of various kinds. All of these subjects were hospitalized; their ages ranged from

TABLE III

ELECTROCARDIOGRAPHIC CHANGES FOLLOWING DIGITALIZATION OF PATIENTS WITH CONGESTIVE FAILURE

PATIENT NO.	DIGITALIS PER CENT	LEAD II				LEAD IV F			
		P-R SEC.	Q-T* SEC.	R-R* SEC.	“K”	P-R SEC.	Q-T SEC.	R-R SEC.	“K”
11	0	0.20	0.353	0.753	0.407	?	unreadable		
	130	0.20	0.333	0.827	0.367	0.16	0.320	0.806	0.352
12	0	?	0.373	0.653	0.463	?	0.366	0.666	0.448
	130	?	0.240	0.353	0.404	?	0.260	0.346	0.450?
13	0	0.16	0.347	0.613	0.443	?	0.353	0.573	0.467
	130	0.18	0.353	0.707	0.420	?	0.360	0.720	0.425
14	0	0.20	0.430	1.087	0.413	0.15	0.440	1.080	0.423
	130	0.24	0.433	1.033	0.426	?	0.420	1.100	0.398
15	0	0.16	0.333	0.700	0.400	?	0.370	0.680	0.448
	130	0.17	0.327	0.700	0.392	?	0.300	0.673	0.366
16	0	0.16	0.400	0.560	0.535	0.14	0.300	0.560	0.403
	130	0.18	0.360	0.740	0.419	0.14	0.340	0.760	0.391
17	0	0.16	0.510	1.287	0.449	0.14	0.500	1.300	0.439
	130	0.16	0.420	1.060	0.407	?	0.473	1.110	0.451
18	0	0.24	0.447	0.840	0.489	0.16	0.427	0.817	0.472
	130	0.20	0.400	0.813	0.443	0.18	0.400	0.800	0.448
19	0	0.24	0.367	0.710	0.436	0.16	0.387	0.720	0.458
	130	0.20	0.310	0.613	0.396	?	0.337	0.623	0.427
20	0	0.14	0.420	1.080	0.404	0.12	0.427	1.080	0.411
	130	0.14	0.323	0.670	0.396	0.16	0.373	0.657	0.462

*Values represent averages of 3 to 5 measurements.

45 to 89 years, and they included seven men and three women. None had received digitalis for at least one month previous to this investigation. The general plan and procedure already described in the study of the normal subjects were followed in this group, except that in a few cases digitalization was carried out in less than five days because of clinical urgency.

RESULTS

The results of the study of this group are summarized in Tables III and IV. From Table III it is apparent that the changes in P-R duration which accompanied the administration of digitalis in therapeutic doses were too small and too inconstant to serve as a measure of the effect of the drug. The value for “K” was fairly consistently, but not uniformly, shorter in Lead II when digitalis was administered; in Lead IV F the value for “K” after digitalis was unchanged in one case, became increased in two others, and was variably shortened in seven. Study of all the electrocardiograms in each patient’s series, however, revealed a lack of progressive change in “K” with increasing doses of digitalis, from which it appeared that this feature did not offer a quantitative indicator of digitalization. In only two of the ten series of

TABLE IV
T-WAVE CHANGES FOLLOWING DIGITALIZATION OF PATIENTS
WITH CONGESTIVE FAILURE

PATIENT NO.	DIGITALIS PER CENT	T WAVES (MM.)			
		I*	II	III	IV F
11	0	± 2.5	-3.0	+3.5	- 2.0
	100	± 2.0	+1.0	+2.0	± 1.0
	130	± 3.0	± 1.0	± 2.0	+ 1.5
12	0	-1.0	-1.5	-0.5	+ 2.0
	100	-2.0	-1.0	-0.5	+ 1.0
	130	+1.5	+1.0	-0.5	+ 1.0
13	0	+1.0	+1.5	+0.5	+11.5
	100	+1.0	+1.5	± 0.5	+ 8.0
	130	+1.5	+1.5	± 0.5	+11.1
14	0	+1.0	+1.5	0.0	± 1.0
	100	+1.0	+2.0	0.0	± 2.0
	130	+1.5	± 1.0	0.0	± 1.5
15	0	± 1.5	+1.0	+3.0	+ 3.5
	100	-2.5	+2.0	+3.0	± 1.5
	130	-3.5	+1.5	+3.0	- 1.5
16	0	± 2.0	+1.5	+2.0	- 4.0
	100	± 2.0	+0.5	+1.0	- 4.0
	130	± 2.0	+0.5	+1.0	- 4.0
17	0	-1.0	+1.0	+1.5	- 4.5
	100	-1.0	0.0	+1.0	- 4.0
	130	-1.0	± 0.5	+1.0	- 5.0
18	0	+2.0	+2.5	-0.5	+ 6.5
	100	+1.5	+2.5	+1.0	+ 2.0
	130	+1.5	+3.0	+0.5	+ 2.0
19	0	+1.0	+1.0	-1.0	± 1.5
	100	± 1.5	-2.0	-3.0	- 1.0
	130	± 1.5	-2.0	-3.0	- 1.5
20	0	0.0	+1.0	+0.5	± 2.0
	100	-2.0	-1.0	+1.0	- 2.0
	130	-2.0	-1.5	+1.0	- 1.5

*Numerals refer to leads.

electrocardiograms were the RS-T segments depressed below their original levels following digitalis. As may be seen from Table IV, the T wave lost amplitude in the records of three patients, and changed from positive to negative in three other cases following digitalis; in the tracings of four patients, on the other hand, T gained in positive amplitude in one or more leads. Similar irregular changes in T were observed in the study of the normal group (see Section I).

No exact correlation between specific electrocardiographic changes and the state of digitalization was seen in these series of records from unselected patients with heart disease. In all but three of the ten cases the original electrocardiograms already exhibited abnormalities of the RS-T segments and T waves, and these may have interfered with the development of digitalis effects.

SECTION III

EFFECTS OF DIGITALIS ON THE ELECTROCARDIOGRAMS OF FIFTY
SELECTED PATIENTS WITH HEART DISEASE

In order properly to investigate the electrocardiographic effects of digitalis on patients with diseased hearts, it was considered necessary to eliminate those whose variety of heart disease was known to be commonly associated with abnormalities of the RS-T segments and T waves. Excluded on this basis were patients more than 50 years of age, and cases of angina pectoris or myocardial infarction. Subjects with hypertension and with lesions of the aortic valves were rejected because their electrocardiograms are known frequently to show RS-T and T-wave abnormalities resembling those caused by digitalis. Also discarded were the records of patients with active rheumatic myocarditis, acute infectious diseases, pericarditis from any cause, advanced renal failure, vitamin deficiency disease, pulmonary embolism, and undiagnosed disease. As a result of such a rigid selection, therefore, the "cardiac group" considered in this study was composed almost entirely of patients with chronic rheumatic heart disease without aortic valvulitis. The material which was finally considered acceptable for study comprised 113 electrocardiograms from 50 patients, and represented about 3.5 per cent of the records obtained in this laboratory from January, 1938, to July, 1940.

For convenience in handling the data, the electrocardiograms were classified as follows:

CLASS	DESCRIPTION
N	Normal adult males
ND	Normal adult males, digitalized
S	Cardiac subjects with sinus mechanism, without digitalis and without failure
SF	Cardiac subjects with sinus mechanism, without digitalis, but in congestive failure
SD	Cardiac subjects with sinus mechanism, digitalized, but not in failure
SDF	Cardiac subjects with sinus mechanism, digitalized and in failure
A	Cardiac subjects with auricular fibrillation, without digitalis and not in failure
AF	Cardiac subjects with auricular fibrillation, without digitalis, but in failure
AD	Cardiac subjects with auricular fibrillation, digitalized, but not in failure
ADF	Cardiac subjects with auricular fibrillation, digitalized and in failure

The following measurements were made in millimeters for all leads:

1. The level of the RS-T junction.
2. The level of the RS-T segments, if such a horizontal level existed (Fig. 1, c); otherwise, the height or depth to which this portion of the curve progressed before the formation of the T wave (Fig. 1, a). Often it was difficult, and sometimes impossible, to differentiate the com-

ponent parts of the RS-T segment and T wave, and the points then measured were taken where abrupt changes in direction occurred, as is illustrated in Fig. 1, *a*. Frequently there was no RS-T segment level (Fig. 1, *b*, *d*) and in the graphs (Fig. 2) the RS-T junction and the crest of T in such instances were joined by a straight line.

3. The amplitude and direction of T. When T was diphasic, the amplitude of the second phase was chosen.

These three points, together with the isoelectric line, were plotted for every electrocardiogram in each group, and the graphic results are presented in Fig. 2.

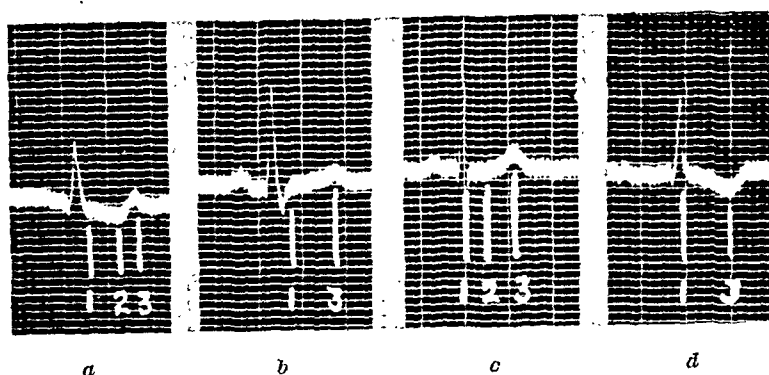


Fig. 1.—Selected reference points for the graphic representation of the RS-T and T variations depicted in Fig. 2: 1, level of RS-T junction; 2, course of RS-T segment, or point of reversal in a diphasic wave, as in *a* (this feature is considered absent in tracings like *b* and *d*); 3, amplitude of T wave, or second phase in a diphasic wave.

Although the criteria for selecting the electrocardiograms representing the “cardiac group” were intended to furnish records that were relatively free from RS-T and T-wave abnormalities which could be attributed to the heart disease itself, it was considered essential actually to establish the pre-digitalization characteristics for this group, rather than assume that they were normal. Accordingly, thirty-three records of patients who had not yet received digitalis were compared with the tracings of ten normal subjects (Section I), and the following minor differences were found:

TABLE V

LEAD	ELECTROCARDIOGRAPHIC FEATURES	NORMAL (10 RECORDS)	CARDIAC (33 RECORDS)
I	Slight elevation of RS-T junction*	30%	3%
	Slight elevation of RS-T segment	60%	3%
II	Slight elevation of RS-T junction	50%	6%
	Slight elevation of RS-T segment	80%	9%
III	Upright T wave	80%	33%
IV F	Slight elevation of RS-T segment	100%	26%

*Slight elevation means usually within the accepted normal limit of 1 mm.

Comment.—The electrocardiograms of the normal subjects showed elevation of the RS-T junction and segment (within the accepted normal limit of 1 mm.) in the majority of cases, whereas those of the cardiac group presented more nearly isoelectric RS-T segments. The T waves in

Leads I and II were upright in all. Our "cardiac group" was therefore regarded as acceptable for the study of digitalis effects. It is interesting, incidentally, that an isoelectric or negative T deflection in Lead III alone, although not considered abnormal, was decidedly more common in the group with heart disease.

The electrocardiographic changes after digitalization were studied in 80 records from patients with heart disease, and compared with the group of 33 tracings from patients who had not received the drug. The most significant differences were as follows:

TABLE VI

LEAD	ELECTROCARDIOGRAPHIC FEATURES	NONDIGITALIZED (33 RECORDS)	DIGITALIZED (80 RECORDS)
II	Slight depression RS-T segment	18%	39%
	Inverted and isoelectric T waves	3%	34%
III	Slight depression RS-T segment	6%	25%
IV F	Slight depression RS-T segment	5%	31%
	Inversion of T wave	0%	10%

Comment.—In only a minority of the records from digitalized patients were the RS-T segments lowered and the T waves inverted. Even these differences between the digitalized and the nondigitalized group were not, however, necessarily an effect of digitalis, for the treated group contained many more patients with grave heart disease, which might itself have introduced these abnormalities into the electrocardiogram.

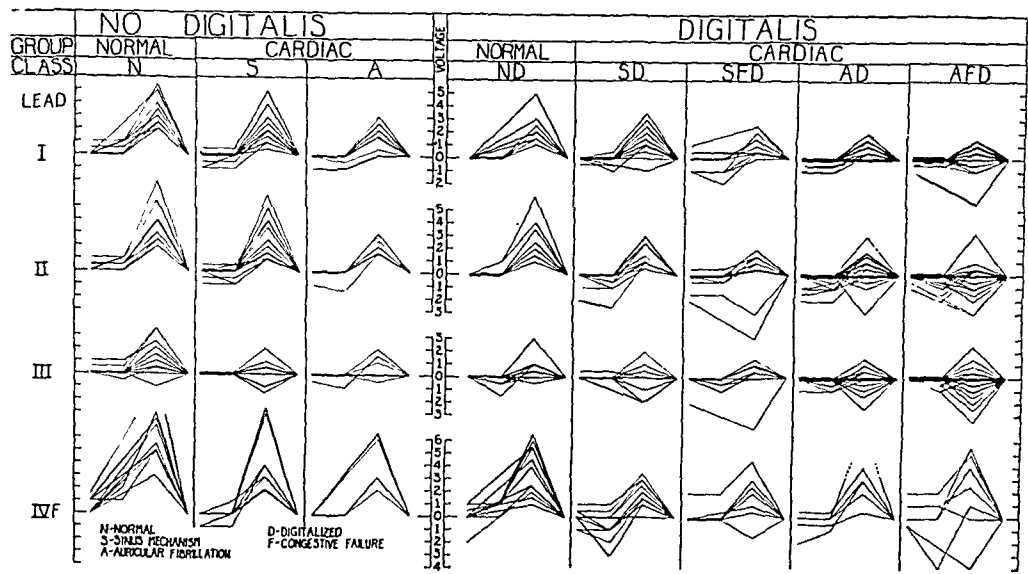


Fig. 2.—Graphic representations of RS-T segments and T waves in the various classes defined in Section III.

The above eighty tracings of digitalized patients included many who had auricular fibrillation, cardiac failure, or both. To eliminate the possible electrocardiographic effects of advanced heart failure and auricular fibrillation, a smaller group which was free from these complications was chosen for study. Twenty-nine electrocardiograms were available on patients with heart disease but no failure or abnormality

of rhythm. Approximately half of these records were from patients who were receiving digitalis. As may be seen from Fig. 2, classes *S* and *SD*, the direction of *T* in both these uncomplicated digitalized and non-digitalized groups was essentially the same. Although it is probable that the depression of the RS-T segment, which appeared particularly in Lead IV F, and the general loss in amplitude of the *T* waves were caused largely by the digitalis, the fact that these rather arbitrary changes were present in less than half the tracings detracts from their usefulness as quantitative indicators of digitalization.

Pursuing further the idea that *T*-wave inversion may be an expression of cardiac disease, rather than a digitalis effect, comparisons of various classes and combinations of classes of heart disease were made, and these data are presented graphically in Figs. 2 and 3 and in tabular form in Table VII.

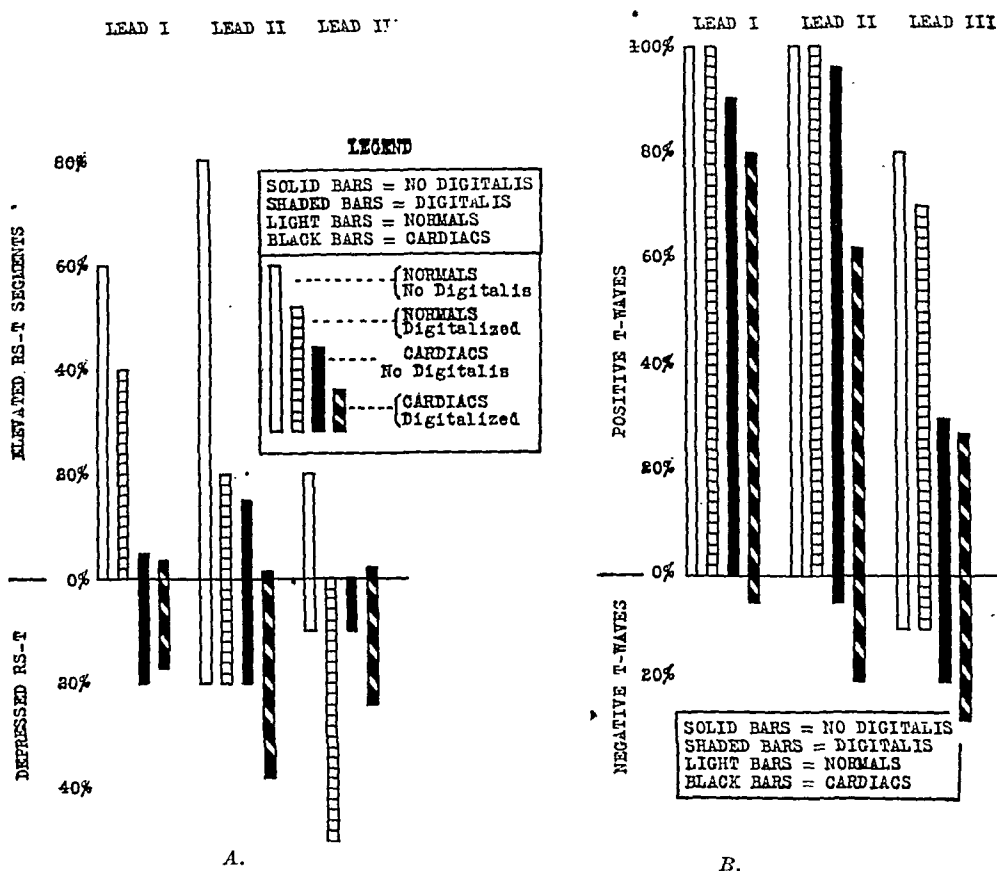


Fig. 3.—A, Frequency of elevation and depression of the RS-T segment, expressed in per cent. The difference between the sum of the positive and negative displacements and 100 per cent represents the incidence of isoelectric RS-T segments. B, Frequency of positive and negative T waves, expressed in per cent. The difference between the sum of the positive and negative waves and 100 per cent represents the incidence of isoelectric T waves.

Fig. 2 is designed to present in a quantitative, graphic form the composite picture of the RS-T and *T* features of the several heart disease classes. It is divided into a "No Digitalis" and "Digitalis" section, each of which is subdivided into selected classes of cardiac disease, ar-

TABLE VII

CLASS	LEAD I				LEAD II				LEAD III				LEAD IV F			
	RS-T		T		RS-T		T		RS-T		T		RS-T		T	
	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
N*	60†	40	0	0	0	0	100	0	0	0	0	0	100	0	0	0
ND	40	60	0	100	0	0	20	80	0	100	0	0	90	10	0	0
S	7	80	13	100	0	0	7	73	20	100	0	0	20	80	0	0
A	0	80	20	90	10	0	0	90	10	100	0	0	20	80	0	0
AF	0	83	17	83	17	0	0	67	33	83	0	17	50	50	0	0
Total	3	82	15	94	6	0	9	75	18	97	0	3	26	68	5	0
SD	7	79	14	86	7	7	0	57	43	100	0	0	20	30	50	0
SFD	20	40	40	90	10	0	10	50	40	80	0	20	30	70	0	15
AD	0	90	10	75	25	0	0	70	30	70	20	10	10	60	30	0
AFD	0	85	15	70	15	15	0	65	35	40	30	30	38	25	37	0
Total	3	83	14	78	16	6	1	60	39	66	16	18	28	44	31	10

*The Class designations are defined in the second paragraph of Section III.

†Figures indicate per cent of records showing these features.

‡The parenthetical figures indicate the number of records represented.

ranged from left to right in an approximate order of increasing abnormality of cardiac function. Inspection of the several classes enables one to observe the probable effects of digitalis, heart disease, auricular fibrillation, and congestive failure upon the RS-T segments and T waves. Table VII represents an analysis of the positive and negative deviations of RS-T and T, and shows the frequency of these deviations in the several heart disease classes.

Examination of Fig. 2 and Table VII, with particular attention to the RS-T segments and T waves, reveals several interesting facts bearing on the effect of digitalis. For example, although depression of the RS-T segment in Lead II was not observed in normal subjects even when they were digitalized, it was already present in 20 per cent of the cardiac patients *before digitalis* was given, and this incidence rose to but 40 per cent when the patients were receiving digitalis. Depression of the RS-T segment in Lead III was found in 50 per cent of the normal digitalized subjects, but in only 25 per cent of the digitalized cardiac patients who did not have failure. Depression of the RS-T segment in Lead IV F appeared in about one-third of the tracings, and seemed, in this lead alone, to be entirely a manifestation of digitalis effect in our "selected cardiac group." In Lead I there was little or no change in this segment following digitalis.

A negative T deflection was rare in Lead I in the digitalized group. In Lead II, inverted T waves occurred infrequently (20 per cent), and almost exclusively in classes complicated by heart failure, regardless of the presence or absence of the digitalis factor. The high incidence of isoelectric T waves in the cases of auricular fibrillation was due, in large part, to the difficulty in measuring T in the presence of coarse fibrillary waves. No positive statement can be made concerning the direction of the T waves in Lead III. It is apparent that flattening or inversion of the T wave seemed to be an expression of heart disease more than of digitalization in any of these classes; this fact is graphically portrayed in Fig. 3.

The presence of auricular fibrillation, unlike congestive failure, was not associated with a greater abnormality of the RS-T segment and T wave, nor did digitalis in the presence of this mechanism show more pronounced effects.

It appears from these observations that, although the electrocardiogram may reveal more or less characteristic changes attributable to digitalis, such effects are inconstant and unpredictable; that similar changes may result from abnormal cardiovascular states aside from digitalis influence; and that the electrocardiogram has, therefore, no general clinical value as a *quantitative* measure of digitalization in the therapeutic range.

SUMMARY AND CONCLUSIONS

Progressive digitalization of ten normal subjects produced electrocardiographic changes which were too small in degree and too incon-

stant in character to indicate any quantitative correlation between the amount of the drug administered and the resultant electrocardiographic effects.

Similar results were obtained in a parallel investigation of ten unselected patients with heart disease and congestive failure.

The study was extended to include more than 100 electrocardiograms from a group of fifty patients who were carefully selected with the expectation that their electrocardiograms would be relatively free from RS-T and T-wave abnormalities which could be attributed to the heart disease itself.

It was observed: (1) that depression of the RS-T segments, with, perhaps consequent, loss in amplitude of the T waves, occurred in less than half of the electrocardiograms of the selected, digitalized patients; (2) that the onset and progression of such changes were neither constant nor uniform accompaniments of the administration of digitalis, and were not quantitatively indicative of the amount of the drug that had been given; (3) that heart disease itself resulted in abnormality of the RS-T segment and T wave quite independent of digitalis effects. This would, of course, have been much more striking if our "cardiac group" had not been selected in such a way as to exclude patients with those lesions which characteristically cause such abnormalities.

We conclude that the electrocardiogram has no practical clinical value for the *quantitative* estimation of the digitalis saturation of patients.

REFERENCES

1. Cohn, A. E., Fraser, F. R., and Jamieson, R. A.: The Influence of Digitalis on the T Wave of the Human Electrocardiogram, *J. Exper. Med.* 21: 593, 1915.
2. White, P. D., and Sattler, R. R.: The Effect of Digitalis on the Normal Human Electrocardiogram, With Especial Reference to A-V Conduction, *J. Exper. Med.* 23: 613, 1916.
3. Pardee, H. E. B.: The Standardization of Digitalis by Its Action on the Human Heart, *J. A. M. A.* 81: 186, 1923.
4. Larsen, K., Neukirch, F., and Nielsen, N. A.: Electrocardiographic Changes in Normal Adults Following Digitalis Administration, *AM. HEART J.* 13: 163, 1937.
5. Stewart, H. J., and Watson, R. F.: The Effect of Digitalis on the Form of the Human Electrocardiogram, With Special Reference to Changes Occurring in the Chest Lead, *AM. HEART J.* 15: 604, 1938.
6. Levy, H., and Boas, E. P.: Clinical Studies of Gitalin and of Digitalis in the Treatment of Auricular Fibrillation, *AM. HEART J.* 15: 643, 1938.
7. Cheer, S. N., and Dieuaide, F. R.: Studies on the Electrical Systole ("Q-T" interval) of the Heart. III. The Effect of Digitalis on Its Duration in the Normal Heart, *Chinese J. Physiol.* 5: 217, 1931.
8. Strauss, H., and Katz, L. N.: Effect of Digitalis on the Appearance of Lead IV, *AM. HEART J.* 10: 546, 1934.
9. Geiger, A. J.: Digitalis U.S.P.XI. Recent Changes in Potency and Designation, *Connecticut M. J.* 4: 331, 1940.
10. Standardization of Precordial Leads; Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland, *AM. HEART J.* 15: 107, 1938.
11. Ashman, R., and Hull, E.: *Essentials of Electrocardiography: Appendix*, New York, 1937, The Macmillan Co.

VARIABLE INTERVAL BETWEEN ELECTRIC AND ACOUSTIC PHENOMENA IN AURICULAR FIBRILLATION

ALDO LUISADA, M.D.
WALTHAM, MASS.

THE time relation between the initial wave of the electrocardiogram and the first heart sound has been studied by many authors, in normal subjects and in patients, and the results have varied considerably. Lewis¹ says that the first sound begins 0.002 to 0.026 sec. after the beginning of R, and 0.011 to 0.039 sec. after the beginning of Q, with a very wide range of time. Lewis' study was done on patients with mitral stenosis and is quoted first because all three patients that I have studied had this disease. In normal subjects, Wiggers and Dean² found that the initial vibrations of the first sound occurred 0.01 to 0.02 sec. after the beginning of R in Lead II, never before the peak of R, and even 0.03 to 0.045 sec. after this peak. Among the recent authors, Cossio³ says that the first sound starts with the apex of R, or 0.01 sec. after it. Calo⁴ says that it can start from 0.02 sec. before the beginning of R to 0.05 sec. afterwards. Leblanc⁵ gives figures of 0.02 to 0.04 sec. after the beginning of the QRS complex, and Caeiro and Orías⁶ 0.008 sec. before the peak of R.

From a short review of the literature it is easy to see that the time relation between initial wave of the electrocardiogram and first sound may vary within a wide range, in normal people as well as in patients. Until now, however, it was thought that, in the same patient under the same conditions, the relation between electric and acoustic manifestations of ventricular systole was fixed, or at least could show only minimal changes. A study of one patient with mitral stenosis showed, on the contrary, some interesting features that will be described below. Therefore, the same study was later repeated on two other patients. The first patient, who showed the more marked changes which are the object of this study, was a 40-year-old man with mitral stenosis, slight heart failure, and auricular fibrillation. The other two patients, who were chosen as controls, were 38 and 48 years of age, respectively, and both had mitral stenosis, slight heart failure, and auricular fibrillation. The study was accomplished with a Stetho-Cardiette (Sanborn). Recording of the standard leads and of the heart sounds from different areas of the precordium was followed, in the third case, by simultaneous recording of heart sounds and venous pulse, and of heart sounds and arterial pulse.

From the Department of Cardiology of the Middlesex University, Waltham, Mass.
Received for publication Nov. 11, 1940.

OBSERVATIONS IN THE FIRST CASE

Even a casual glance at the record of this patient (Fig. 1) shows that the QRS wave is followed by the first sound after a time which is quite different in the different systoles. Because the slow, initial vibrations of the first sound were confused with the vibrations caused by the diastolic murmur when diastole was short, it was possible only to measure the distance between apex of the Q wave and beginning of the ample, quick vibrations of the first sound. This distance varied from 0.03 to 0.07, and was sometimes more than twice that of the other systoles (see Table I). By measuring the distance between the first,

TABLE I

(THE FIRST PART REFERS TO FIG. 1, THE REST TO ANOTHER RECORD, NOT REPRODUCED; BOTH ARE FROM CASE 1.)

DISTANCE IN SECONDS BETWEEN THE PRECED- ING R WAVE AND THE R WAVE STUDIED (SYSTOLE & DIASTOLE)	DISTANCE IN SECONDS BETWEEN THE APEX OF THE R WAVE AND THE FIRST QUICK VIBRATION OF THE FIRST SOUND (DELAY)	DISTANCE IN SECONDS BETWEEN THE FIRST QUICK VIBRATION OF THE FIRST SOUND AND THE FIRST QUICK VIBRATION OF THE SECOND SOUND (SYSTOLE)
1. ----	0.030	0.310
2. 0.75	0.030	0.320
3. 0.47	0.070	0.220
4. 0.43	0.070	0.220
5. ----	0.030	0.280
6. 0.68	0.040	0.300
7. 0.76	0.020	0.300
8. 0.74	0.035	0.320
9. 0.44	0.060	0.235

large, quick vibration of the first sound and the first, large, quick vibration of the second sound, i.e., the length of ventricular systole, it was found that this, too, changed from 0.31 to 0.22 sec. When diastole was long, the R wave was followed by a short interval before the first sound, and by a long systole. On the contrary, when diastole was short, the R wave was followed by a delayed first sound, and by a short systole. The shortening of systole was such that even by adding the longer delay it could not reach the length of the normal systole.

OBSERVATIONS IN THE SECOND AND THIRD CASES

In the second case, the first sound started with one or two slow vibrations which were quite distinct from those of the diastolic murmur, even when diastole was short. It was possible, therefore, to calculate a double figure, i.e., that from the apex of Q to the beginning of the slow vibrations, and that from the apex of Q to the beginning of the quick vibrations. The result is shown in Fig. 2 and in Table II. When the diastole which preceded QRS was long, the time between the electric and acoustic waves was short. On the contrary, when diastole was short, the delay became longer. This fact was less evident than in Case 1,

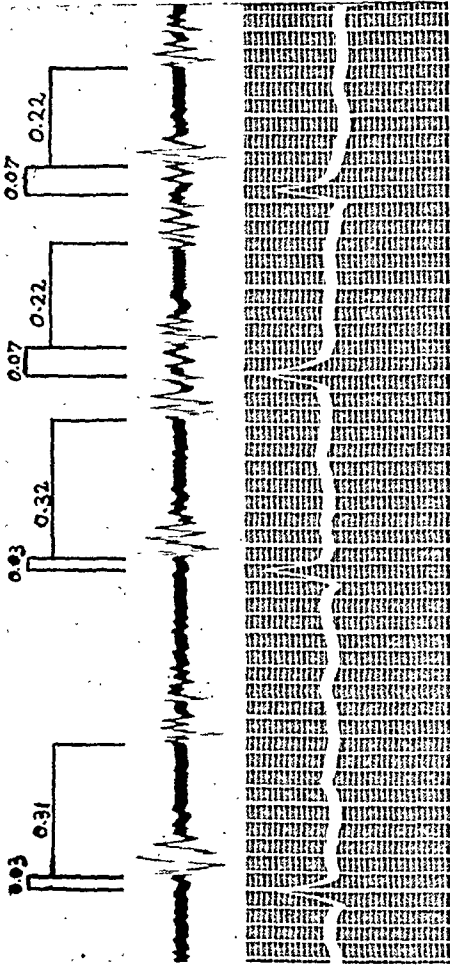


Fig. 1.—First patient, aged 40. Upper curve: Heart sounds, with usual microphone at the third left intercostal space. Lower curve: Lead II of the EKG. First sound delay and length of systole are marked on the top.

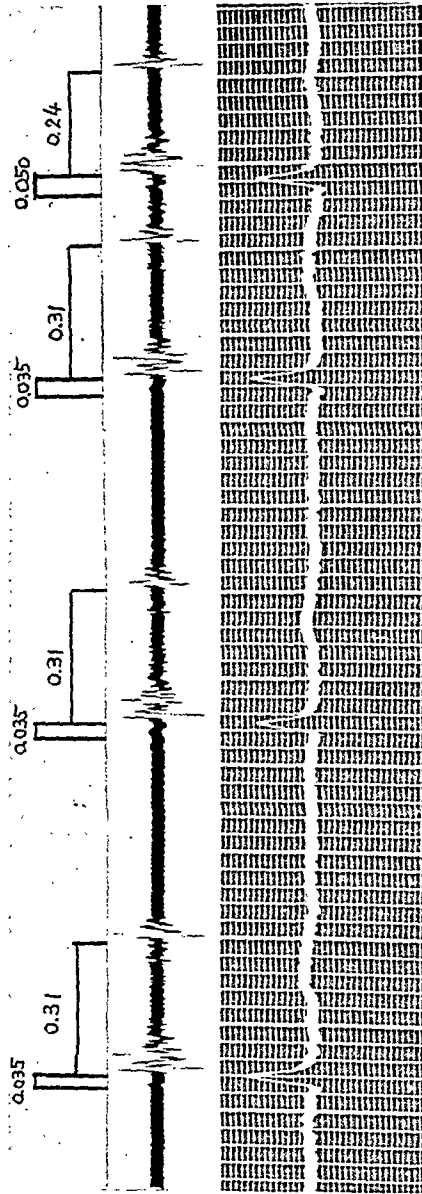


Fig. 2.—Second patient, aged 38. Upper curve: Heart sounds, with special microphone at the apex. Lower curve: Lead I of the EKG. Indications as in Fig. 1.

but was still present, as well for the slow as for the quick vibrations. The length of systole was also markedly shorter when the preceding diastole was shorter.

In the third case, the time between the Q wave and the first sound was practically the same in all systoles, and even the length of the systoles showed only slight changes in spite of the arrhythmia (Fig. 3, Table II).

TABLE II

(THE FIRST PART CONCERNS CASE 2, AS SHOWN IN FIG 2; THE SECOND PART CONCERNS CASE 3, AS SHOWN IN FIG. 3.)

DISTANCE IN SECONDS BETWEEN THE PRECED- ING R WAVE AND THE R WAVE STUDIED (SYSTOLE & DIASTOLE)	DISTANCE IN SECONDS BETWEEN THE FIRST VIBRATION OF THE FIRST SOUND AND THE APEX OF THE Q WAVE (DELAY)	DISTANCE IN SECONDS BETWEEN THE FIRST QUICK VIBRATION OF THE FIRST SOUND AND THE FIRST QUICK VIBRATION OF THE SECOND SOUND (SYSTOLE)
	SLOW VIBRAT.	QUICK VIBRAT.
1. ----	-0.02	+0.035
2. 0.82	-0.02	+0.035
3. 0.80	-0.02	+0.035
4. 0.47	0.00	+0.050
1. ----		0.060
2. 0.96		0.060
3. 0.60		0.070
4. 0.62		0.060
5. 0.61		0.065

These facts made it possible to check up on the occurrence of an interesting feature of the pulse. It is known that in cases of auricular fibrillation the pulse is typically irregular, and that the waves travel with different speeds. When the delay between QRS and the peripheral pulse was measured, it was found to be longer for the smaller waves than for the others. My observation of a difference in the delay between QRS and first sound suggests that the delay between QRS and pulse was the result of a real delay in the mechanical part of systole, and not of a slower speed of the wave. Fig. 4 shows that the second wave, which was much smaller, had a longer delay after the first sound than the other waves. Therefore, the slower speed of the smaller waves was real, and not an artifact.

DISCUSSION

The observation that there was a difference in the delay between QRS and the first sound in the different systoles of a patient with auricular fibrillation led to an investigation of two other patients of a similar age, with the same functional disability and the same heart lesion. The variability of the delay occurred in a lesser degree in the second case, and not at all in the third. One explanation is that, when diastole is shorter, the first sound has a different type of vibrations because the isometric

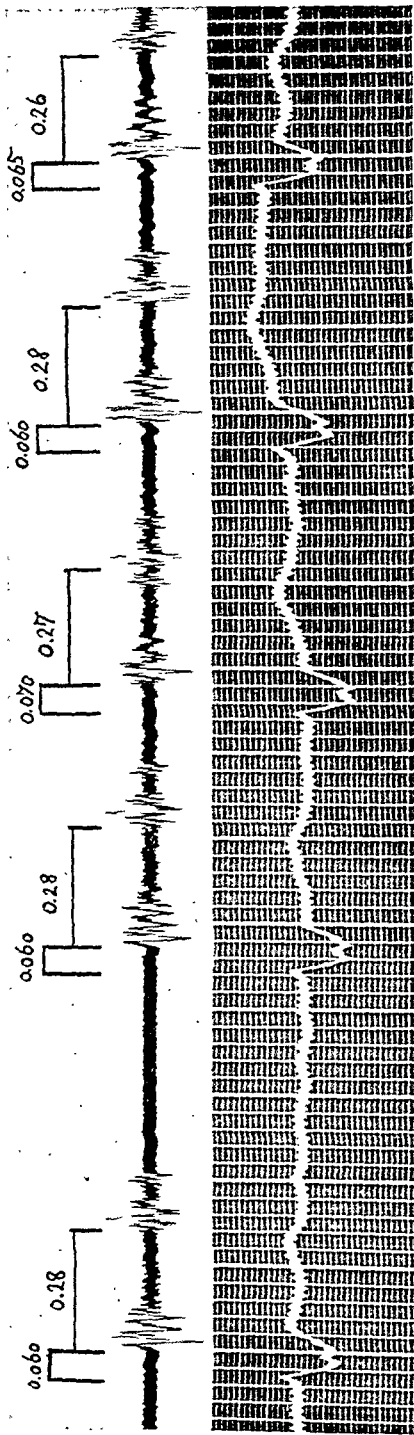


Fig. 3.—Third patient, aged 48. Upper curve: Heart sounds, with usual microphone at the third left intercostal space. Lower curve: Lead I of the EKG. Indications as in Fig. 1.

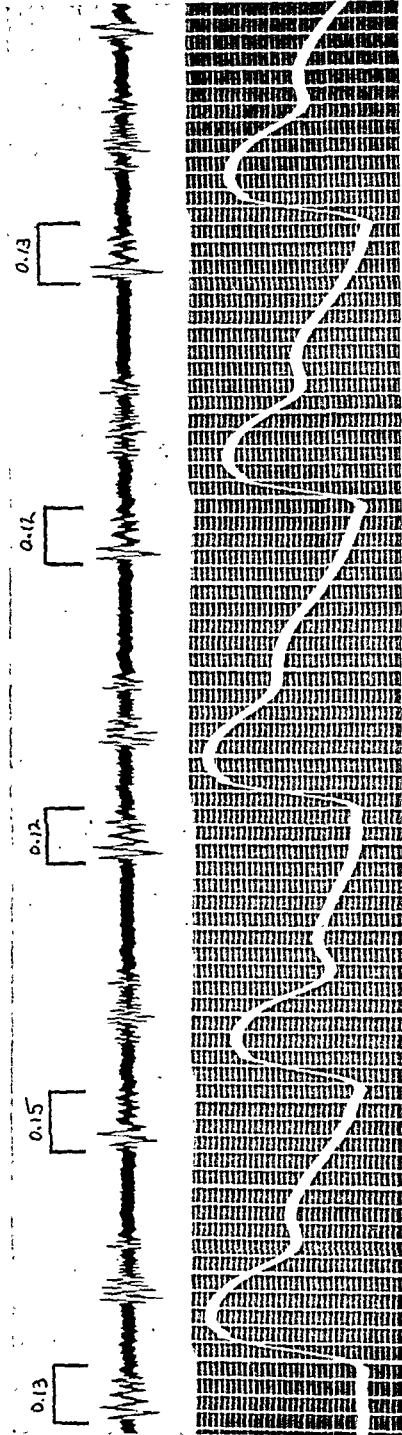


Fig. 4.—Third patient. Upper curve: Heart sounds at the aortic area. Lower curve: Brachial pulse. First sound-brachial pulse delay is marked.

contraction of the ventricles is longer. It could be supposed that the first, slow vibrations would be more prolonged, and that only the quick, high vibrations would be delayed. A study of this was not possible in the first case, but in the second case, in which there was also some change in the delay, a complete study was made, and showed a similar delay in the slow vibrations. The suggestion was at best only hypothetical, because the quick vibrations are already occurring during the isometric contraction of the ventricles (Orías and Braun Menéndez⁷).^{*} We shall admit, then, that, in some cases of auricular fibrillation, when diastole is very short, the contraction of the ventricles is slightly delayed. This differing relationship between the electric and acoustic waves seems to point to the possibility of a dissociation between excitation and contraction of the ventricles. When this occurs it has a useful effect, for it allows longer filling of the ventricles when diastole is very short.

We also studied the length of ventricular systole, as shown by the distance between the first and second sounds. It was observed that, in Cases 1 and 2, systole was short when the preceding diastole was shorter. This well-known difference, which seems quite logical, is, however, not constant, as it was not present in Case 3. It can be suggested that, in some cases, part of the diastole is not accompanied by real filling of the ventricles, as most of it occurs during the early phase of quick filling. Differences in the length of diastole could then be accompanied by a nearly constant filling of the ventricles, and by a nearly constant length of the systoles.[†]

The speed of transmission of the pulse waves was studied only in the third case, for in this case there were no great differences in the delay between excitation and contraction of the ventricles. Moreover, inasmuch as the speed of the smaller pulse waves was slower, it is clear that that fact could not be attributed to the phenomenon which is newly described here.

SUMMARY

A case of auricular fibrillation in which the interval between QRS and the first heart sound was much longer after a short diastole is described.

Two more cases were studied, in one of which the same phenomenon occurred. The length of systole changed in proportion to that of the preceding diastole in the two cases in which the interval between the electric and acoustic phenomena was variable.

Measurement of the pulse wave speed by means of the heart sounds does not change the known fact that smaller waves have a slower speed in cases of auricular fibrillation.

^{*}Moreover, in some systoles the slow vibrations started before the Q wave. It is, therefore, probable that they were caused by some presystolic vibration of the mitral valve, unless an isoelectric phase of QRS was present.

[†]The observation that the length of the interval between the first and second sound changes often in auricular fibrillation was first made by Battaerd.⁸ In his tracings the interval varied between 0.28 and 0.34 sec.

REFERENCES

1. Lewis, T.: The Time Relations of Heart Sounds and Murmurs With Special Reference to the Acoustic Signs in Mitral Stenosis, *Heart* 4: 241, 1912/1913.
2. Wiggers, C. J., and Dean, A. L.: The Nature and Time Relations of the Fundamental Heart Sounds, *A. J. Physiol.* 42: 476, 1917.
3. Cossio, P.: *Aparato circulatorio*, Buenos Aires, El Ateneo, 1939.
4. Calo, A.: *Atlas de Phonocardiographie Clinique*, Paris, Masson et cie, 1938.
5. Leblanc, M. A.: Quoted by Orías and Braun Menéndez.
6. Caeiro, A., and Orías, O.: *Rev. Arg. de Cardiol.* 4: 71, 1937.
7. Orías, O., and Braun Menéndez, E.: *The Heart Sounds in Normal and Pathological Conditions*, London, Oxford Univ. Press, 1939.
8. Battaerd, P. Y. T. A.: Further Graphic Researches on the Acoustic Phenomena of the Heart in Normal and Pathological Conditions, *Heart* 6: 121, 1915/17.
9. Lian, C., and Welti, J. J.: Le premier bruit du coeur normal, *Arch. d. mal. du coeur.* 31: 320, 1938.
10. Weiss, O., and Joachim, G.: Die Beziehungen der Herztöne und Herzgeräusche zum EKG. *Deut. med. Woch.* 36: 2187, 1910 (II).
11. Wolferth, C. C., and Margolies, A.: The Influence of Auricular Contraction on the First Sound and the Radial Pulse, *Arch. Int. Med.* 46: 1048, 1930.
12. Frédéricq, H.: *Aspects actuels de la Physiologie du Myocarde*. Paris, Presses Univ., 1927.

FURTHER OBSERVATIONS ON THE EFFECTS OF CERTAIN
XANTHINE COMPOUNDS IN CASES OF CORONARY
INSUFFICIENCY, AS INDICATED BY THE RE-
SPONSE TO INDUCED ANOXEMIA

NORMAN E. WILLIAMS, M.D., HENRY A. CARR, M.D.,
HOWARD G. BRUENN, M.D., AND ROBERT L. LEVY, M.D.
NEW YORK, N. Y.

IN A PREVIOUS paper¹ a method was presented for studying the effect of various drugs on the coronary circulation in man. The patients breathed a mixture of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes, or until the complaint of discomfort made it desirable to terminate the induced anoxemia. The time of appearance of pain and the sum of the deviations of the RS-T segments of the four-lead electrocardiogram were compared in controls and after medication was given. The report was based on observations made in ten cases of coronary insufficiency.

One of the drugs studied was theophylline with ethylenediamine (aminophyllin). It was found that after its administration, either by vein or orally, the time of appearance of pain during induced anoxemia was materially prolonged, and RS-T deviation was diminished. The T waves of the electrocardiogram were also modified, but these changes were not subject to accurate quantitative comparative measurement and therefore were disregarded. It was concluded that aminophyllin, when taken by mouth in adequate doses, exerts a beneficial action in certain cases of cardiac pain by causing dilatation of the coronary vessels. The result, it was stated, probably depends, in part, upon the anatomic and physiologic state of the coronary circulation. These vary in different patients, and in the same person from time to time.

The literature dealing with the therapeutic action of the xanthines in cases of disease of the coronary arteries, and on coronary blood flow in experiments on animals, was reviewed. Three relevant papers have since been published. Essex and his collaborators,² using the thermistoruhr, found that, after intravenous injection of aminophyllin in trained, unanesthetized dogs, the coronary flow was increased from 15 to 173 per cent. The degree of increase was not proportional to the size of the dose, which ranged from 11.5 to 32 mg. per kg. The duration of the effect was from two to twenty-four minutes after injection. Using a flow meter, Green,³ confirming the work of a number of others, observed that the intravenous injection of 20 to 50 mg. of aminophyllin in dogs

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Medical Clinic of the Presbyterian Hospital.

This investigation was aided by a grant from the Josiah Macy, Jr. Foundation.

Received for publication Nov. 22, 1940.

produced an increase in coronary flow which was due to coronary dilatation. In his opinion, the xanthines, like the nitrites, act as coronary dilators, but their effectiveness may be diminished by their concomitant augmentation of cardiac work. Stewart and Jack⁴ injected aminophyllin intravenously in man, in doses of 0.48 Gm. The peripheral blood flow was increased for a few minutes. There was also an increase in cardiac output, of a degree sufficient to provide for the increase in peripheral flow, without redistribution of the circulating blood volume.

In view of the relatively small number of cases included in our previous study, and because it seemed desirable to make comparable observations on the action of other xanthine derivatives, the present work was undertaken. In addition to aminophyllin, which was given by mouth and by vein, the following drugs were included: Theophylline with sodium acetate, by mouth and by vein, and theobromine with sodium acetate, by mouth. As before, lactose, taken orally, and physiologic salt solution, given intravenously, served as controls.

PROCEDURE

The tests were conducted as described in our earlier paper.¹ They were performed in the cardiologic laboratory, at least one hour after the last meal, with the room quiet and at a comfortable temperature. Before beginning, the patient rested on the bed for not less than twenty minutes. The tests were done, as nearly as possible, at weekly intervals. At least one control anoxemia test^{5, 6} was done in every case before the drug study was begun. In five cases, such a test was given on completion of the drug series, and after all medication had been omitted for a week. No change was made in the customary mode of life of the patients, and they were permitted to continue the use of nitroglycerin for the relief of anginal attacks; but nitroglycerin was not taken for at least one hour preceding a test.

The patients were unaware of the nature of the preparations given. At the end of each week, during which a remedy was taken orally, the patient expressed his opinion as to its effect upon his attacks of pain, and reported any unpleasant symptoms. He was asked also whether there was any modification in his response to effort, how many nitroglycerin tablets were used, and whether any emotional or economic upsets had occurred which might have a bearing upon his condition. All of his answers were noted and charted.

DRUGS AND DOSAGE

Theophylline With Ethylenediamine (Aminophyllin).—For oral use, this was put into capsules in the hospital pharmacy, each containing 0.18 Gm. (3 gr.).* One capsule was taken three times daily after meals for one week. In the previous study, the same amount was given four times a day. The dose for intravenous injection was 0.48 Gm. (7½ gr.) in 20 c.c. of normal salt solution.† The injection was made into a cubital vein during a five-minute period. An electrocardiogram was taken five minutes before the injection and another five minutes after its completion. The anoxemia test was then started.

*Made by Lederle Laboratories, Inc. This is said to contain not less than 70 per cent of the theophylline.

†Made by Byk-Guldenwerke, Berlin, Germany, and called Metaphyllin. This was part of a pre-war supply on hand. The theophylline content is not stated on the package.

No drugs, except nitroglycerin as needed, were taken during the week preceding the intravenous injections. This rule obtained not only for aminophyllin, but for all substances given by vein.

*Theophylline With Sodium Acetate.**—Enteric-coated tablets were given orally three times a day after meals for one week. Each tablet contained 0.18 Gm. (3 gr.). During one week, the individual dose was one tablet; during a second week it was two tablets (0.36 Gm.). Intravenously, 0.48 Gm. in twenty c.c. of sterile salt solution was injected, using the same technique as described for aminophyllin.

Theobromine With Sodium Acetate.†—Enteric-coated tablets were given orally. During one week, one tablet of 0.45 Gm. (7½ gr.) was given four times daily, after meals and at bedtime. During a second week, two tablets (0.9 Gm.) were given three times daily after meals.

Lactose.—This was employed as a control for the drugs given by mouth. It was prepared in capsules of 0.2 Gm. each, resembling in appearance those containing aminophyllin. The patients received one capsule three times a day for a week, in each course.

Physiologic Salt Solution.—This served as a control for the drugs injected intravenously. In each case, 20 c.c. were given by vein, according to the technique described for aminophyllin.

MATERIAL (TABLE I)

Observations were made on ten patients, three of whom were used as subjects in our previous drug study. In all, the diagnosis was coronary sclerosis with anginal pain. All of them were regarded as having moderately advanced disease, as indicated

TABLE I

CLINICAL MATERIAL

TEN PATIENTS WITH CORONARY SCLEROSIS AND ANGINAL PAIN

CASE NO.	HOSPITAL UNIT NO.	AGE (YR.)	SEX	COLOR	ADDITIONAL DIAGNOSIS	CONTROL EKG.	CARDIAC ENLARGEMENT
1	589726	66	M.	Wh.	Hypertension	Normal	+
2	295520	59	F.	Col.		Normal	+
3	360149	65	M.	Wh.	Healed myocardial infarct	Abnormal	+
4	376063	70	M.	Wh.		Abnormal	0
5	216669	55	F.	Wh.		Normal	0
6	591058	57	F.	Wh.	Hypertension	Normal	0
7	367410	47	M.	Wh.		Normal	0
8	477070	65	M.	Wh.		Normal	0
9	285886	42	M.	Wh.	Healed myocardial infarct	Normal	0
10	357651	46	F.	Col.		Normal	0

by the severity and frequency of attacks, as well as by physical and electrocardiographic examination. None of the patients suffered from congestive heart failure; and none was tested who had had an attack of coronary occlusion within four

*The tablets and the solution for intravenous injection were supplied by the Upjohn Company, through the kindness of Dr. A. Garrard Macleod. The theophylline content was said to be always 60 per cent of the labelled dose. Roentgen studies in man have shown that 91 per cent of 144 tablets passed through the stomach intact, and, of these, 91 per cent disintegrated in the small intestine. Only five entered the colon intact, and not one was recovered from the feces (Pharmaceutical Bulletin No. 113, prepared by the Upjohn Company). The composition of the enteric coating is not given.

†These tablets were supplied by Brewer and Company, Inc. The enteric coating, it is stated, is made of whale wax. Roentgen studies on man have shown that 97 per cent of the tablets disintegrate promptly in the first portion of the small intestine (personal communication from the Brewer Company). These tablets are said to contain not less than 63 per cent of theobromine.

months. They took no drugs, other than those prescribed for the study, during the period of these observations. They were chosen because they were well known to us, having been under observation in the outpatient department or in the hospital wards, or both, over a period of months or years. They were of average intelligence and were cooperative.

In age, they ranged from 42 to 70 years. Six were white men. Of four women, two were white and two colored. Two had healed myocardial infarcts; coronary occlusion had occurred at least a year before these tests were carried out. One man and one white woman had hypertension. During the latter part of the study, the woman, while at home, suffered from an attack of acute coronary occlusion, so that administration of several of the drugs had to be omitted in her case. Two men and one colored woman had enlarged hearts. All had had spontaneous attacks of anginal pain for at least six months; in each case, the oral use of nitroglycerin afforded a measure of relief. In eight, the control electrocardiogram was normal;

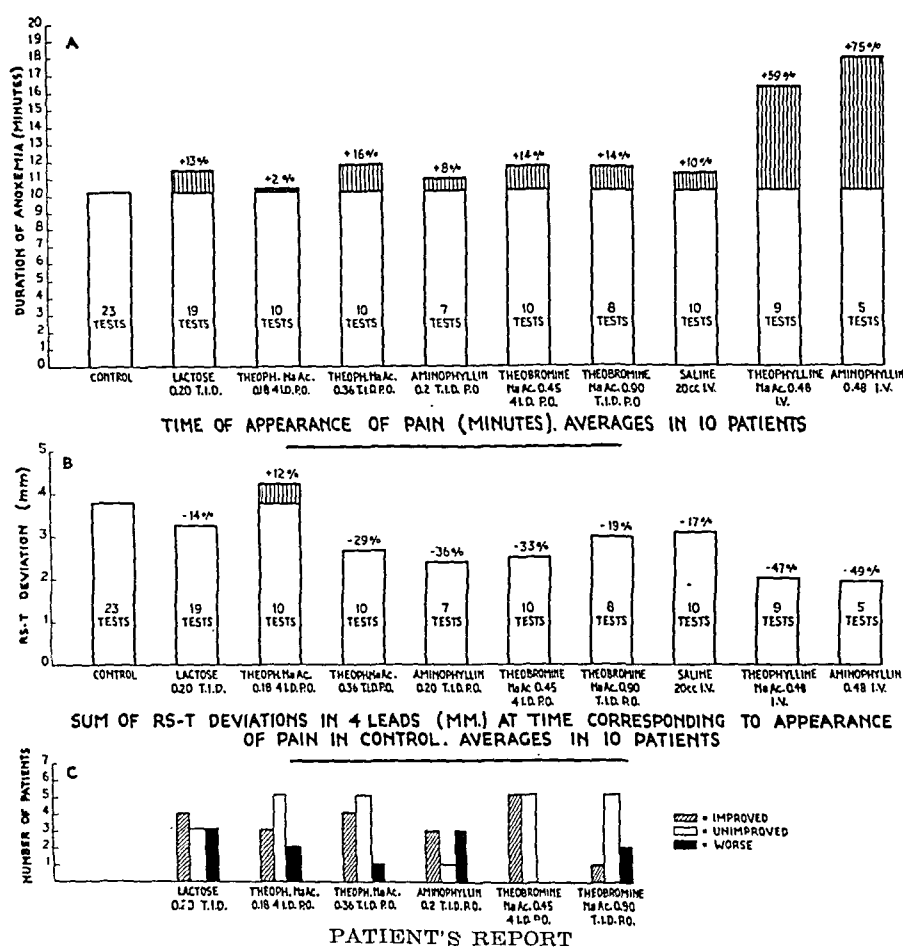


Fig. 1.—A, Modifying effect of drugs on the time of appearance of cardiac pain caused by induced anoxemia. B, Modifying effect of drugs on deviation of the RS-T segments caused by induced anoxemia. C, Modifying effect of drugs, orally administered, upon symptoms. Each drug was given for a period of one week.

in two it was abnormal. All showed positive control anoxemia tests.^{5,6} Eight of the ten experienced pain in less than twenty minutes during the control tests; two were able to breathe a 10 per cent oxygen mixture for the full period without discomfort, although significant changes occurred in the form of the electrocardiograms.

TABLE II
EFFECTS OF DRUGS, TAKEN BY MOUTH

DRUG	INDIVIDUAL DOSE (gm.)	INDIVIDUAL TESTS (NUMBER)									
		TIME OF ONSET OF PAIN			DEGREE OF RS-T DEVIATION			PATIENT'S SYMPTOMS			UN-CHANGED
		DELAYED	HASTENED	UN-CHANGED	DECREASED	INCREASED	UN-CHANGED	IMPROVED	WORSE	UN-CHANGED	
Aminophyllin	0.20	3	3	1	6	1	0	3	3	1	1
Theophylline with sodium acetate	0.18	1	3	6	5	4	1	3	2	5	5
Theophylline with sodium acetate	0.36	5	3	2	9	0	1	4	1	5	5
Theobromine with sodium acetate	0.45	4	2	4	8	2	0	5	0	5	5
Theobromine with sodium acetate	0.90	2	4	2	6	2	0	1	2	5	5
Lactose	0.20	4	0	14	7	0	11	7	5	7	7

The results are based upon 105 tests and measurements of 775 four-lead electrocardiograms.*

RESULTS (FIG. 1)

Because the functional state of the coronary circulation in a given person is subject to spontaneous variation, the results in the ten cases were pooled, averaged, and charted. In this way trends became apparent. The effects in the individual cases are also given in the text and in Table II.

Theophylline With Ethylenediamine (Aminophyllin), by Mouth.—Seven patients received this drug. In this group there was no significant delay in the onset of pain (8 per cent). The deviation of the RS-T segments was diminished by 36 per cent. In the individual cases, the onset of pain was delayed in three; it occurred earlier than in the control in three; and in one no change was noted. RS-T deviation was decreased in six cases and increased in one. In three instances the patient reported a lessening of symptoms during the week; in one there was no change; and in three the discomfort increased.

Theophylline With Ethylenediamine, by Vein.—This was given to five patients. In this group the onset of pain was delayed by 75 per cent. RS-T deviation was diminished by 49 per cent. In the individual cases, the onset of pain was delayed in three and occurred earlier than in the control in one. In the fifth case, the patient experienced no pain during the control test, or after receiving the drug. RS-T deviation was diminished in all five cases.

Theophylline With Sodium Acetate, by Mouth. A. Dose—0.18 Gm., Four Times a Day.—This was given to ten patients. In the group, there was no significant delay in the onset of pain (2 per cent). RS-T deviation was increased by 12 per cent. In the individual cases, the onset of pain was delayed in one; in three, pain occurred earlier than in the control; in six, there was no change. RS-T deviation was increased in five, decreased in 4, and unchanged in one. In three instances the patient reported lessening of symptoms; in five there was no change; and in two the discomfort increased.

B. Dose—0.36 Gm., Three Times a Day.—This was given to ten patients. In this group the onset of pain was delayed by 16 per cent. RS-T deviation was decreased by 29 per cent. In the individual cases, the onset of pain was delayed in five and occurred earlier than in the control in three, and in two there was no change. RS-T deviation was decreased in nine cases; no change was observed in one. In four instances the patient reported a lessening of symptoms; in five there was no change; and in one the discomfort increased.

*All four leads of the electrocardiogram were taken while pain was present, if it occurred. The complete record can be made in from one to two minutes, and prolongation of anoxemia for this length of time was found to be without hazard.

The precordial lead used was the one designated as IV F by the American Heart Association. All electrocardiograms were read independently by at least two observers.

Theophylline With Sodium Acetate, by Vein.—This was given to nine patients. In this group the onset of pain was delayed by 59 per cent. RS-T deviation was decreased by 47 per cent. In the individual cases, the onset of pain was delayed in seven; the other two patients were able to breathe the 10 per cent oxygen mixture for the full twenty minutes without discomfort. RS-T deviation was diminished in all of the nine cases.

Theobromine With Sodium Acetate, by Mouth. A. Dose—0.45 Gm., Four Times a Day.—This was given to ten patients. In this group the onset of pain was delayed by 14 per cent. RS-T deviation was decreased by 33 per cent. In the individual cases, the onset of pain was delayed in four; in two pain occurred earlier than in the control; and in four there was no change. RS-T deviation was decreased in eight and increased in two. In five instances, the patient reported improvement; in five there was no change; and in none was the discomfort increased.

B. Dose—0.9 Gm., Three Times a Day.—This was given to eight patients. In this group the onset of pain was delayed by 14 per cent. RS-T deviation was decreased by 19 per cent. In the individual cases, the onset of pain was delayed in two; it occurred earlier than in the control in four; and in two there was no change. RS-T deviation was decreased in six cases and increased in two. In only one instance did the patient report improvement; in five there was no change; and in two the discomfort increased.

Lactose, by Mouth.—This was given to ten patients on nineteen occasions. In the entire series of tests, the onset of pain was delayed by 13 per cent. RS-T deviation was decreased by 14 per cent. In the individual cases, the onset of pain was delayed in four tests on four patients. RS-T deviation was decreased in twelve tests on seven patients. In seven instances the patients reported improvement; in seven there was no change; and in five the discomfort increased.

Physiologic Salt Solution, by Vein.—This was given to ten patients. In this group the onset of pain was delayed by 10 per cent. RS-T deviation was decreased by 17 per cent. In the individual cases, the onset of pain was delayed in two; in three, pain occurred earlier than in the control; and, in five, there was no change. RS-T deviation was decreased in seven; in three there was no change.

UNPLEASANT DRUG EFFECTS

The unpleasant symptoms ascribed by the patients to the various drugs, when they were taken orally, are shown in Table III. Insomnia, nausea, and abdominal discomfort were the most frequent complaints. In a dosage of 0.36 Gm. four times a day, theophylline with sodium acetate, in all but one case, caused so much insomnia and gastrointestinal distress that the evening dose was discontinued. For the same reason, the larger dose of theobromine with sodium acetate (0.9 Gm.) was re-

TABLE III
UNPLEASANT EFFECTS OF DRUGS TAKEN BY MOUTH

DRUG	NUMBER OF PATIENTS	DOSAGE	UNPLEASANT EFFECTS	
			NUMBER OF PATIENTS COMPLAINING	SYMPTOMS
Aminophyllin	7	0.20 Gm. t.i.d.	3	1 anorexia 1 nausea 1 swelling and aching of face; aching of teeth and gums; nausea and vomiting
Theophylline with sodium acetate	10	0.18 Gm. 4 i.d.	4	2 anorexia 1 nausea; gas 1 insomnia; heartburn
Theophylline with sodium acetate	10	0.36 Gm. t.i.d.	5	2 insomnia; abdominal pain; gas 1 insomnia; abdominal pain; gas; vomiting 1 nausea; vomiting 1 swelling and aching of face; aching of teeth and gums; nausea and vomiting
Theobromine with sodium acetate	10	0.45 Gm. 4 i.d.	4	1 anorexia 1 nausea 1 flatulence; belching 1 palpitation
Theobromine with sodium acetate	8	0.90 Gm. t.i.d.	6	2 insomnia; abdominal discomfort 2 vomiting 1 insomnia 1 nausea; flatulence
Lactose	10 (19 tests)	0.20 Gm. t.i.d.	3	1 nausea; vertigo 2 abdominal pain

duced from four to three times daily. In one case (Case 6), both aminophyllin and theophylline with sodium acetate caused swelling and aching of the face, aching of the teeth and gums, and nausea and vomiting. The patient was not affected by theobromine sodium acetate. Apparently, in this instance, there was a true idiosyncrasy to theophylline. This is a rare occurrence. Because of the severe toxic reaction, she was not given either of the theophylline preparations by vein.

On a number of occasions, after the intravenous injection of aminophyllin or theophylline with sodium acetate, the patients complained of a sense of warmth. No untoward reactions were encountered.

DISCUSSION

It is of some practical importance to know whether therapeutic doses of the xanthine compounds dilate the coronary vessels in man, and so may be expected to afford relief to patients with anginal pain. That relatively large amounts, when injected intravenously into normal animals,

will cause an increase in coronary flow has been abundantly demonstrated. The evidence for a similar and more sustained effect in patients with coronary sclerosis who have taken various members of this group by mouth has been conflicting.

In our earlier study,¹ using the same objective method employed in the observations just described, it was demonstrated that aminophyllin exerted such an action. It is significant that, with this drug, the results with respect to the degree of RS-T deviation in 1939 and 1940 show such close agreement (Table IV). When given by vein, the decrease in RS-T deviation was 58 and 49 per cent; the delay in the onset of pain in the 2 series was, respectively, 63 and 75 per cent. When given by mouth, the decrease in RS-T deviation was 32 and 36 per cent; the delay in the onset of pain was, respectively, 26 and 8 per cent. The effect on pain was less in the 1940 series of patients, who suffered, as a group, from a more advanced state of disease. They received only three doses a day, as compared to four doses in the 1939 series. But, objectively, the degree of coronary dilatation produced, as indicated by decrease in RS-T deviation, was similar in the two groups.

Lactose, when given by mouth, caused a delay in the onset of pain, in the two series of cases, of 2 and 13 per cent respectively; the decrease in RS-T deviation was 13 and 14 per cent. This degree of variation in RS-T deviation, as previously pointed out,¹ must be regarded as the approximate error of the method.

Because of the similarity of these two sets of observations, we feel justified in stressing the significance of the effects of theophylline with sodium acetate and theobromine with sodium acetate which were noted under comparable circumstances. The delay in the onset of pain, as was the case in the 1940 group with aminophyllin, was not striking, but

TABLE IV
COMPARISON OF ACTION OF AMINOPHYLLIN AND LACTOSE IN STUDIES OF 1939 AND 1940

DRUG	DATE	NUMBER OF TESTS	DELAY IN ONSET OF PAIN (PERCENTAGE CHANGE)	DECREASE IN RS-T DEVIATION IN EKG. (PERCENTAGE CHANGE)
Aminophyllin (by vein)	1939	10	63	58
	1940	5	75	49
Aminophyllin (by mouth)	1939	14	26	32
	1940	7	8	36
Lactose (by mouth)	1939	10	2	13
	1940	18	13	14

the decrease in RS-T deviation produced by theophylline with sodium acetate, in individual doses of 0.36 Gm., and by theobromine with sodium acetate, in doses of 0.45 Gm., was comparable to that obtained with aminophyllin, namely, 29 and 33 per cent, respectively. Apparently, theophylline with sodium acetate in the smaller dose of 0.18 Gm. was ineffectual. The larger dose of theobromine with sodium acetate, 0.9 Gm., caused toxic effects in so many of the cases that the beneficial action, if any, was masked.

In general, patients with less severe and less frequent attacks of pain showed a better therapeutic response than those in the more advanced stages of illness. This was well exemplified in the same patient at different times (Fig. 2). This man had suffered from attacks of anginal pain for ten months before the first drug study was made, in 1938. At that time, walking slowly for a distance of one to four blocks induced characteristic discomfort which was relieved by nitroglycerin. On two

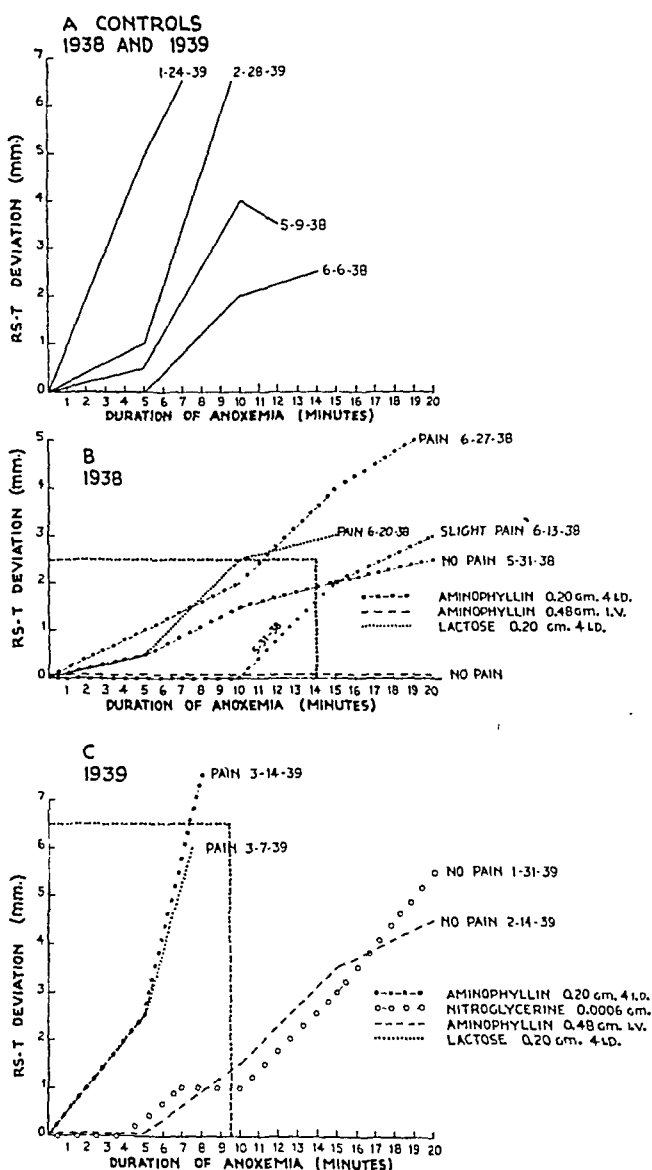


Fig. 2.—(Unit No. 542971) The response of a 54-year-old Japanese chef to induced anoxemia, with and without the modifying effects of drugs, during two studies made six months apart. He had had attacks of anginal pain for ten months. A, Control anoxemia tests. B, The modifying effect of lactose and aminophyllin during May and June, 1938. C, The modifying effect of lactose, nitroglycerin, and aminophyllin during January, February, and March, 1939. (The rectangle outlined by the broken lines, shown in Figs. 2, 3, 4, and 5, represents each patient's optimal response to induced anoxemia. It is derived by taking from the several control tests the longest time he could endure anoxemia and the smallest amount of RS-T deviation observed, regardless of whether they were noted in the same test.)

occasions, after taking aminophyllin for a week, the RS-T deviation was diminished, respectively, by 24 and 36 per cent. During these two weeks, the need for nitroglycerin decreased from four to ten tablets daily, to one or two a week. In January and February, 1939, his toler-

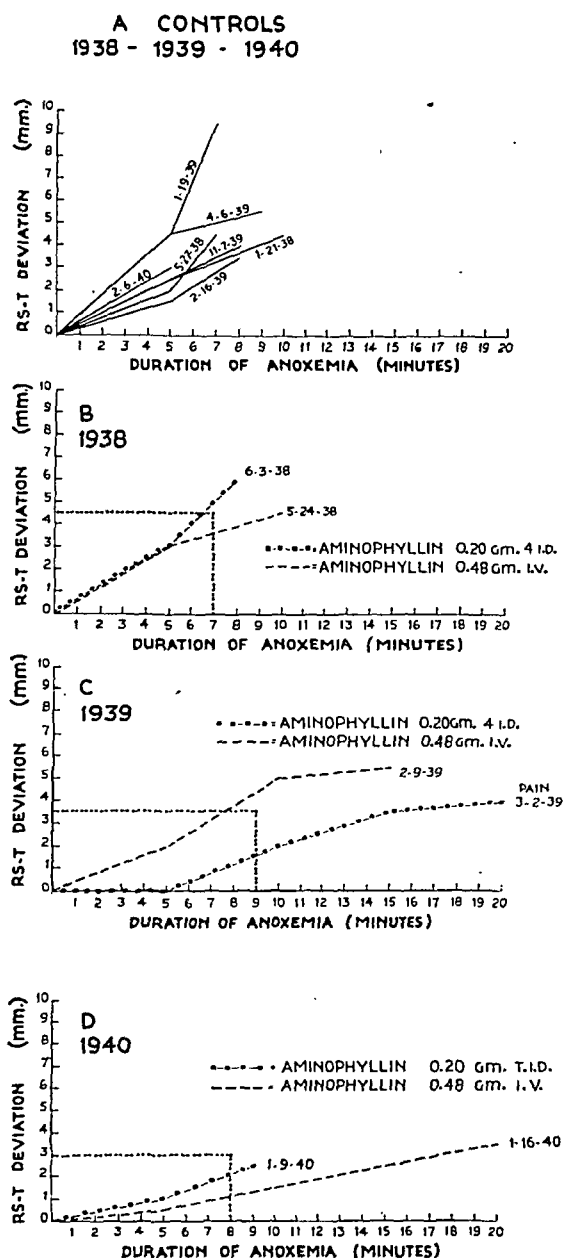


Fig. 3.—Case 4, (Unit No. 376063) The response of a 70-year-old, white, stationary engineer to induced anoxemia, with and without the modifying effect of drugs given in the course of three studies conducted over a period of two years. He had had attacks of anginal pain for eight years. *A*, Series of control tests performed in the period from January, 1938, to February, 1940. *B*, Modifying effect of aminophyllin in 1938. *C*, Modifying effect of aminophyllin in 1939. *D*, Modifying effect of aminophyllin in 1940.

ance for the 10 per cent oxygen mixture was less than it had been six months previously, and the modifying effects of aminophyllin were correspondingly diminished. In fact, at this time aminophyllin was wholly ineffectual by mouth, although it still exerted its action when injected

intravenously. He was aware of the change in his condition and complained that medication did not afford relief as it had the preceding summer.

In contrast to this decrease in effectiveness, coincident with aggravation of symptoms, are the records of the patient which are shown in Fig. 3. His response to anoxemia was studied in 1938, 1939,

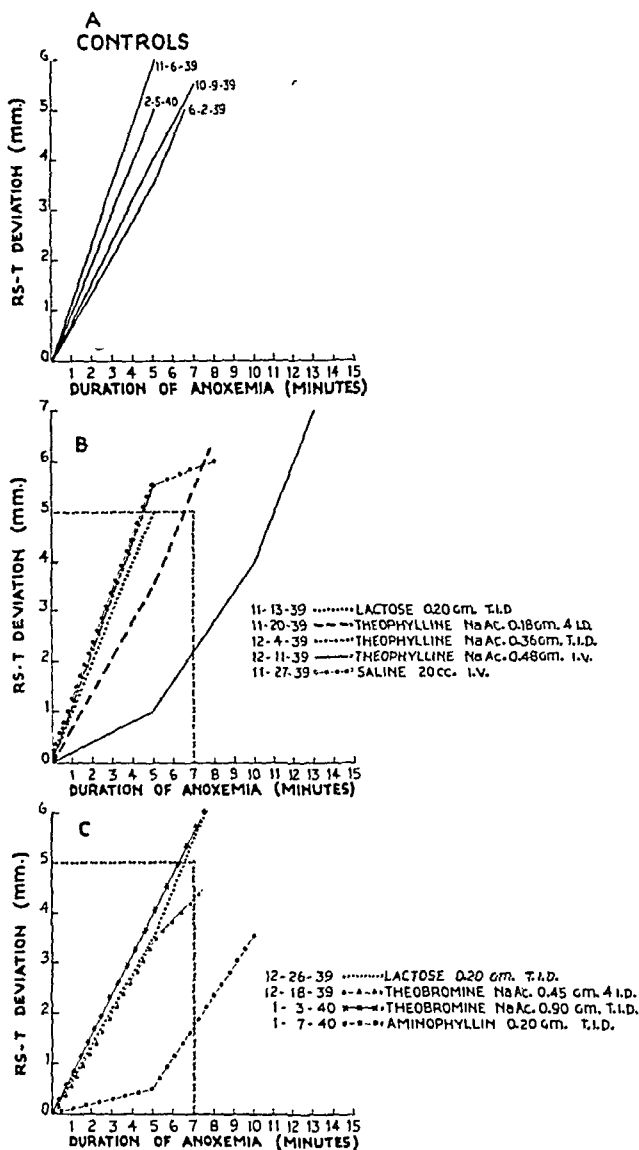


Fig. 4.—Case 9, (Unit No. 285886) The response of a 42-year-old, white, taxicab driver to induced anoxemia, with and without the modifying effect of drugs. He had had attacks of anginal pain for nine years. Myocardial infarction occurred in November, 1938. A, Control tests. B and C, Response to anoxemia, as modified by drugs.

and 1940. The effects of aminophyllin by mouth and by vein are charted. The rectangles marked off by the broken lines in B, C, and D show an increase in tolerance to the 10 per cent oxygen mixture during the period from 1938 to 1940. This is apparent from the progressive

decrease in RS-T deviation. Aminophyllin, when given intravenously, became gradually more effective; given by mouth, the same trend was apparent, but to a lesser degree. The patient's symptoms, as shown by his reaction to ordinary physical activity, showed no noteworthy change in the course of these two years; the responses to effort and to the action of the drug were not parallel. In Fig. 3C, it appears that when amino-

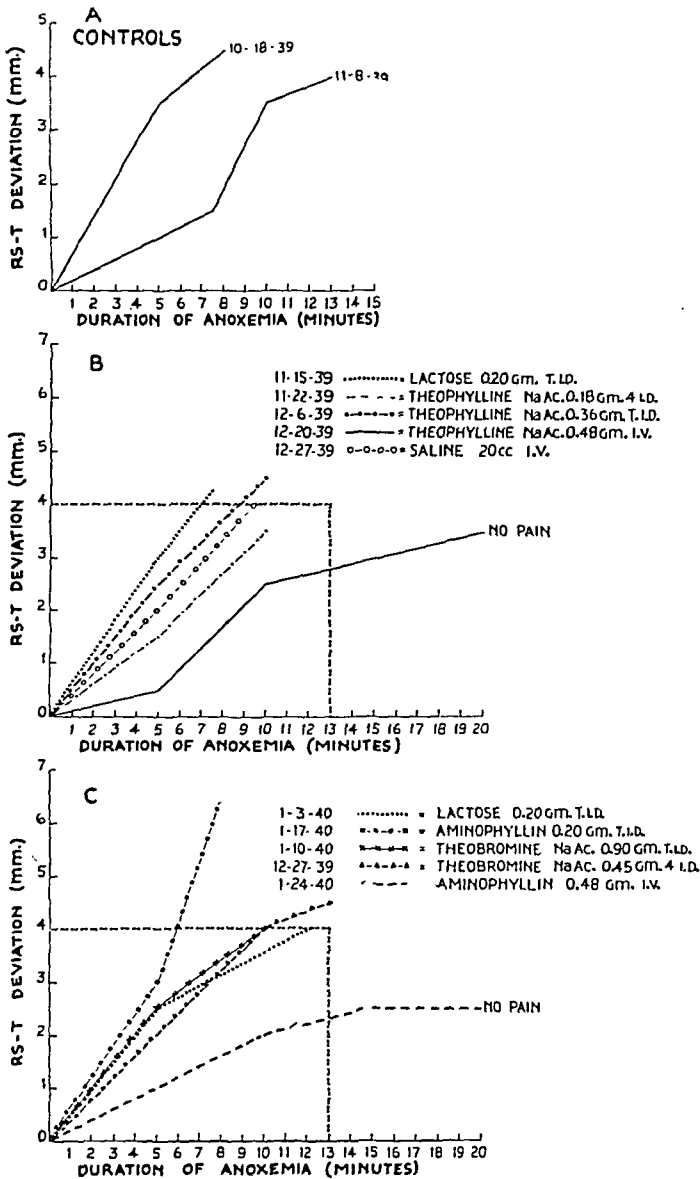


Fig. 5.—Case 7, (Unit No. 367410) The response of a 47-year-old, white, male cornet player to induced anoxemia, with and without the modifying effect of drugs. He had had attacks of anginal pain for six years. *A*, Control tests. *B* and *C*, Response to anoxemia, as modified by drugs.

phyllin was taken by mouth it was more effective than when injected intravenously. This unusual response was observed in two other cases. Its explanation is not clear.

None of the ten patients reacted favorably to all of the drugs; and none of the drugs, in any of the dosages employed, was effective in all

of the cases. The variation in the individual human reaction to various medicinal remedies is well known; it makes impossible the prediction of what the therapeutic result will be in any given instance. The character and extent of the lesions in the coronary arteries undoubtedly determine, in a measure, the effectiveness of treatment.

In Figs. 4 and 5 are charted the response in Cases 7 and 9 to each of the drugs studied. In Case 7, none of the drugs was effective by mouth, but aminophyllin, by vein, modified the response to anoxemia. Of the drugs taken orally by Patient 9, only aminophyllin exerted any demonstrable action.

From the point of view of ability to induce coronary dilatation, as shown by decrease in RS-T deviation, aminophyllin in individual doses of 0.20 Gm., theophylline with sodium acetate in doses of 0.36 Gm., and theobromine with sodium acetate in doses of 0.45 Gm. were about equally effective when given by mouth. None of them, in this series of cases, materially modified the time of appearance of pain caused by induced anoxemia. The effect on the patients' symptoms was variable and difficult to appraise accurately.

SUMMARY AND CONCLUSIONS

1. Aminophyllin, theophylline with sodium acetate, and theobromine with sodium acetate were administered to ten patients with coronary sclerosis and anginal pain. The two theophylline compounds were given both orally and by vein; the theobromine derivative was given only by mouth. Lactose, given orally, and physiologic salt solution, injected intravenously, served as controls.

2. The response to induced anoxemia, employing a technique previously described, was used as an index of the action on the coronary circulation. The effects on the sum of the RS-T deviations in the four-lead electrocardiogram and on the time of appearance of pain were the criteria used; the former, because it was an objective index, was stressed as the more important.

3. Aminophyllin, in doses of 0.20 Gm., three times a day, theophylline with sodium acetate, in doses of 0.36 Gm., four times a day, and theobromine with sodium acetate, in doses of 0.45 Gm., four times a day, were about equally effective, when given orally, in causing a decrease in RS-T deviation. None of them, in this series of cases, materially modified the time of appearance of pain caused by induced anoxemia. In a previous study, aminophyllin, in doses of 0.2 Gm., given orally four times a day, delayed the time of onset of pain; the dose was larger and the symptoms and signs of coronary insufficiency in the former group of patients were not so marked.

4. After intravenous injection, the decrease in RS-T deviation and the delay in the onset of pain were about the same for equal doses of aminophyllin and theophylline with sodium acetate.

5. In general, patients with less severe and less frequent attacks of pain show a better therapeutic response than do those with more advanced coronary insufficiency, but a patient who responds favorably to one xanthine compound does not necessarily show a similar reaction to others; and, in some cases, no effect is demonstrable.

6. When given orally in proper dosage to certain patients with coronary sclerosis, compounds of theophylline and theobromine dilate the coronary arteries and bring about symptomatic improvement. The choice of suitable subjects and of the most effective preparation in the individual case must depend, for the present, on clinical trial.

REFERENCES

1. Levy, R. L., Bruenn, H. G., and Williams, N. E.: The Modifying Action of Certain Drugs (Aminophyllin, Nitrites, Digitalis) Upon the Effects of Induced Anoxemia in Patients with Coronary Insufficiency, *AM. HEART J.* 19: 639, 1940.
2. Essex, H. E., Wegria, R. G. E., Herrick, J. F., and Mann, F. C.: The Effect of Certain Drugs on the Coronary Blood Flow of the Trained Dog, *AM. HEART J.* 19: 554, 1940.
3. Green, H. D.: Effect of Pitressin, The Nitrites, Epinephrine and the Xanthines on Coronary Flow in Mammalian Hearts, *Blood, Heart and Circulation*, Publication of the American Association for the Advancement of Science No. 13, Science Press, 1940, p. 105.
4. Stewart, H. J., and Jack, N. B.: The Effect of Aminophyllin on Peripheral Blood Flow, *AM. HEART J.* 20: 205, 1940.
5. Levy, R. L., Bruenn, H. G., and Russell, N. G., Jr.: The Use of Electrocardiographic Changes Caused by Induced Anoxemia as a Test for Coronary Insufficiency, *Am. J. M. Sc.* 197: 241, 1939.
6. Levy, R. L., Williams, N. E., Bruenn, H. G., and Carr, H. A.: The "Anoxemia Test" in the Diagnosis of Coronary Insufficiency, *AM. HEART J.* 21: 634, 1941.

Department of Clinical Reports

CONSTRUCTIVE PLEURITIS AND PERICARDITIS

C. SIDNEY BURWELL, M.D., AND G. DARRELL AYER, M.D.

BOSTON, MASS.

THE purpose of this paper is to place on record the case of a patient who exhibited an instructive and (so far as can be found) hitherto unreported complication of tuberculous pericarditis with constriction.

REPORT OF CASE

The patient, a 54-year-old laborer of Lithuanian birth, began in January, 1938, to suffer from coryza and cough. A few weeks later he became conscious of shortness of breath on exertion, and soon after this had dyspnea at rest, orthopnea, and swelling of the ankles. On March 12, about two months after the onset of his symptoms, he entered the Peter Bent Brigham Hospital.

At this time he had mild dyspnea when at rest. The heart rate was rapid, the rhythm regular, the pulse small. The heart was not enlarged and no murmurs were heard. The arterial blood pressure was 100/70 mm. Hg, and the venous blood pressure was 210 mm. of water. The cervical veins were visibly distended; the edge of the liver was felt 5 cm. below the costal margin; and there were signs of fluid in both pleural cavities and slight edema of the ankles. A friction rub was audible in the left axilla. At the fluoroscopic examination the excursion of the left border of the heart was considered to be less than normal, and there was no visible movement of the right border. An electrocardiogram showed low voltage, inversion of T_2 and T_3 , and a normal Lead IV.

Marked improvement in comfort followed a few days of hospital care, during which time his chest was tapped and he received digitalis and mercurial diuretics. When he had lost about 16 pounds of fluid by various routes he could lie flat without dyspnea and his vital capacity was 3,100 c.c., but the peripheral venous pressure remained elevated. The basal cardiac output was measured by the acetylene method and found to be 2.2 liters per minute. The output per beat was 29 c.c. The total plasma protein was 6.5 to 7.2 (albumin 2.9 to 3.5). The temperature rarely rose above 99° F. and was usually within limits which were considered normal. The pleural fluid had a specific gravity of 1.010; there were 1,000 cells per c.mm., 98 per cent of which were small lymphocytes.

The combination of congestion of the systemic circulation, essentially clear lungs, and a small, underactive heart suggested that he had constrictive pericarditis. The greatly diminished cardiac output, the persistence of the elevation in venous pressure, and the fluoroscopic observations were regarded as compatible with this diagnosis. It appeared to be a kind of pericardial disease which is most frequently seen as the result of tuberculosis; when a guinea pig which was inoculated with the patient's pleural fluid died of tuberculosis, the etiology was considered to be established.

After a period of observation in the ward, pericardiectomy was advised, but the patient decided against operation at that time and left the hospital April 23, 1938.

From the Departments of Medicine and Pathology, Harvard Medical School and the Peter Bent Brigham Hospital, Boston, Mass.

Received for publication April 29, 1940.

At home, for the ensuing ten weeks, he was up and about. The situation changed but little during this time; the degree of disability remained about the same, the venous pressure remained high, and edema accumulated unless mercurial diuretics were administered. On one occasion during this period a pleural friction rub was heard on the *right* side.

Because of the lack of improvement, operation was again suggested, and, on July 11, 1938, the patient entered the surgical service of the Peter Bent Brigham Hospital. The operation was performed by Dr. Elliot C. Cutler on July 13, 1938. He recorded the following description of the operation.

"There was a minimum of evidence of inflammatory disease in the areolar tissue between the sternum and the pericardium. The pericardium itself was tough and thick, fully 3 mm. in thickness. It was opened, and a cleavage plane found between the pericardium and the epicardium. Gradually the heart was separated from adherent pericardium, using Joker scissors, the knife, and periosteal elevator. Then the whole anterior portion of pericardium was removed. When this had been done the muscle pulsed much more vigorously, but even then a dense epicardial scar seemed to hold back the muscle considerably. I tackled this with sharp dissection with a new knife, for by no other means could I lift this scar away from the muscle, and, even so as I dissected I was sometimes shaving off bits of muscle. It was a tedious job; and I did not feel I had removed all of the epicardial scar, but at least a considerable amount came away."

The tissue which was removed showed, microscopically, dense hyaline cicatricial tissue in which occasional proliferative tubercles were embedded.

When the venous pressure was measured a few hours after operation it was found to have been reduced to normal. It fluctuated a little for the following week, but after that was never above 105 mm. of water, and was usually less than 90 mm. of water. The venous distension was visibly reduced, as was the volume of the liver. These observations indicated that the obstruction to filling of the heart had been removed by the operation.

Nevertheless, during the first week after operation he accumulated fluid in his pleural cavities and required tapping on four occasions. The fluid was greenish or amber, clear, and had a specific gravity of 1.014 to 1.018. Two weeks after operation he returned to the medical service for observation.

At this time his only discomfort was pain in the region of the wound on inspiration. There was a little fluid in each pleural cavity, but no other suggestion of congestion. His temperature (which during the week after operation had reached 103°) went as high as 100° only once. He was discharged after a week. He felt a little weak and still had slight precordial pain.

At home he found, to his disappointment, that he did not gain strength or weight. Attempts to increase his bodily activity caused severe pain in the region of his operative wound and a consciousness that he could not take a deep breath. Eight weeks after operation he was again admitted to the medical ward.

Examination at this time showed no evidence of venous distension, enlargement of the liver, or edema. The venous pressure was 96 mm. of water, the arterial pressure, 120/95 mm. Hg, and the circulation time, seventeen seconds. Fluoroscopic examination of the heart showed large hilar shadows, a small heart beat and indistinct borders, and a visible, but small, excursion of the right border. These observations were accepted as indicating that the mechanical obstruction of the constricting pericardium had been relieved by pericardiectomy.

He suffered, however, from a new and distressing disability—a grave interference with respiratory movements and a sense of inability to get his breath. He did not have orthopnea. Inspiration was sharply limited, and the vital capacity was only 600 c.c., although there was no evidence of pulmonary congestion or edema. The trachea was firmly fixed so that it did not move with respiration or deglutition.

There was a sense of difficulty in swallowing. Vigorous attempts at inspiration failed to lift the sternum and led to an apparent sucking in of the apices. Under the fluoroscope the diaphragm appeared to be not paralyzed, but fixed. The sternum did not lift, but there was some expansion of the lower chest outward, and the ribs moved upward a little. The anteroventral part of the costal margin moved inward; the axillary part, outward. Certain peculiar additional waves in the electrocardiogram were found to be linked with the recurrent muscular effort of inspiration.

These abnormalities were taken to point to a mechanical limitation of chest mobility, probably caused by involvement of the mediastinum and diaphragm in scar tissue, and not by heart failure or constriction. The ecchymosis which still surrounded the operative wound, now over two months old, was attributed to rupture of small vessels in the scar tissue by his frantic efforts to expand his chest.

He had also at this time several attacks of tachycardia with palpitation. On one such occasion electrocardiograms revealed nodal tachycardia, with a ventricular rate in the neighborhood of 200. There was some discussion of the possibility of releasing the chest surgically from whatever was preventing its expansion. This was decided against. The respiratory distress continued, and the patient died suddenly (he was found dead in bed a few minutes after he had been observed in no more than his usual discomfort) on Sept. 25. This was nine months after the onset of his symptoms and two and one-half months after the operation on his pericardium.

The description of the significant portions of the post-mortem examination is as follows:

Thorax.—As the anterior aspect of the thorax was opened, the heart was found to be firmly bound to the sternum by dense cicatricial tissue. A similar scar bound the anterior surface of both lungs to the chest wall. With the single exception of the cicatrix at the site of the operation on the pericardium, these collections of cicatricial tissue were confined to their respective serous cavities, and did not merge with one another or extend outside the parietal layers.

In the superior mediastinum the fat overlying the great vessels was free from active inflammation or induration. A large fibrotic lymph node bound the anterior surface of the trachea (at its bifurcation) firmly to the pericardium covering the posterior surface of the right atrium.

Pericardium.—Between the heart and the sternum there was a mass of cicatricial tissue occupying the area of decortication. In this mass, in an area beneath the fourth rib on the left, there was a small pocket containing 3 c.c. of yellow, puriform material. Tubercle bacilli were obtained from this material by smear and by culture. With that exception there was no gross evidence of active inflammation in the pericardium. The two pericardial layers were bound together by cicatricial tissue that filled the space but measured no more than 2 mm. in thickness (Fig. 1). This scar tissue and the heart beneath it were easily compressible. Unfortunately, no attempt was made to judge its capacity to stretch.

Pleura.—On both sides, tuberculous granulation tissue, with the gross appearance of a cicatrix, covered the visceral and parietal pleural surfaces in a continuous, thin layer. For the most part the two layers were fused, but inferiorly, on each side, a small cavity, containing about 30 c.c. of yellow, gelatinous fluid, remained between the layers (Fig. 2).

Lungs.—Through the thin pleural cicatrix the lungs were easily compressible and crepitant throughout. When the apices were sectioned no scars or active tuberculous lesions were seen. Several fibrosed, black, lymph nodes appeared along the larger bronchioles, but there was no caseation or calcification. Posteriorly, in each lower lobe, there was slight atelectasis, but elsewhere the lungs were well aerated, and pink frothy fluid was obtained on pressure. The vessels were free from thrombi.

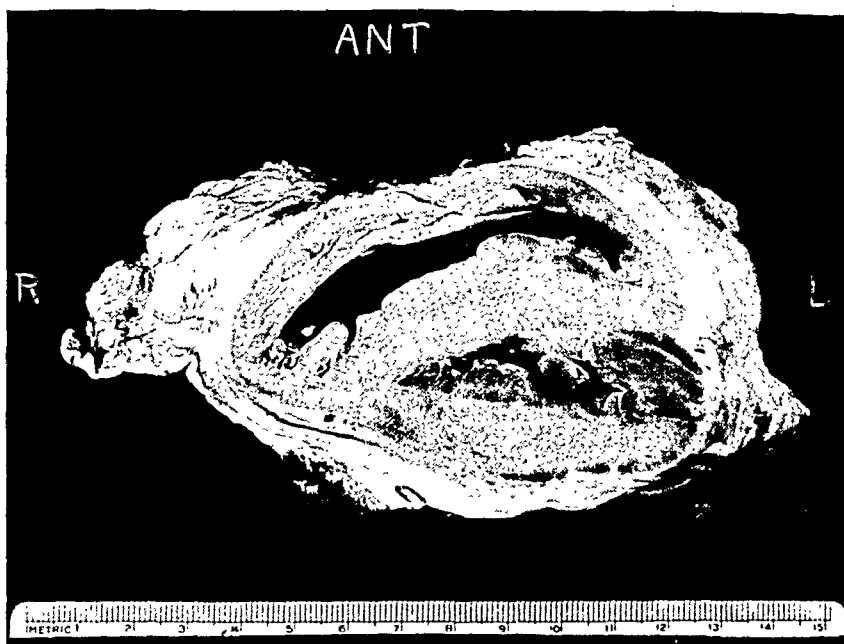


Fig. 1.—Heart and pericardium in cross section. Anteriorly, all of the cicatrix that lay between heart and sternum has been cut away. The surface on the left of the specimen is the rough pleural cicatrix which was cut across to free the heart. This gives an outer, dark layer. Next is a pale layer of extrapericardial fat, and then a dark stratum which is the tuberculous granulation tissue between the visceral and parietal pericardium. The next white stratum is the normal epicardial fat with the coronary vessels, and beneath this lies myocardium.

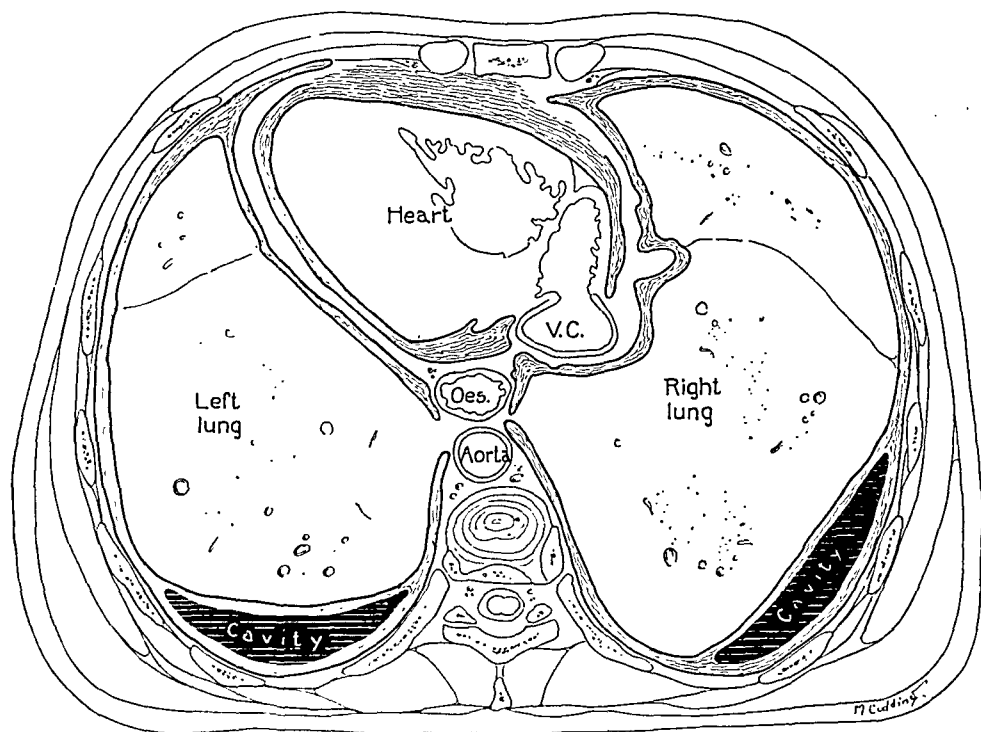


Fig. 2.—Diagrammatic cross section of the lower thorax to show the complete envelopment of the lungs by a continuous sheet of scar tissue. The tuberculous cicatrices are indicated by broken wavy lines which are drawn somewhat wider than they actually were. Posteriorly, the pleural cicatrices are separated by collections of fluid, labeled cavity. Elsewhere the two layers are fused. They are confined to their respective serous cavities except in the operative site anterior to the heart, where the postoperative cicatrix extends from the heart to the sternum.



Fig. 3.—Left lung and pleura (hematoxylin and eosin stain, $\times 15$). On the right are normal intercostal fat and nerves. To the left of this is the pleural cicatrix, and then the atelectatic peripheral portion of the lung. Below is the upper extension of the persisting pleural cavity at the left base. The thick tuberculous granulation tissue covers the pleural surfaces and fuses above to obliterate the cavity. The clear areas are active tubercles. There is no tuberculosis in the lung.



Fig. 4.—Lung and pleura near apex (hematoxylin and eosin stain, $\times 15$). The obliteration of the pleural space has left many small irregular cavities filled with dark amorphous debris. About these is a pale collar of active tuberculous granulation tissue which shades into the denser cicatrix. The lung tissue and the intercostal fat are free from inflammation or cicatrization.

Heart.—Cross sections through the heart showed that the wall of the left ventricle measured 1.6 cm. in thickness, and that of the right, 1.1 cm. The valves were all normal. The superior and inferior venae cavae entered the right atrium without suffering a reduction of their caliber by the surrounding cicatrix.

The other viscera were normal in size and gross appearance. The brain was slightly edematous, but there was no evidence of inflammation or hemorrhage.

Microscopic Examination.—The lungs showed moderate edema, as evidenced by acidophilic granular material in the alveolar spaces. There were a few scattered microscopic areas of early bronchopneumonia. In the areas of atelectasis the alveolar walls were slightly thickened with connective tissue, and the alveolar spaces contained macrophages filled with carbon pigment and fat droplets. About four small cicatrices were found near bronchioles. These were thought to be healed tuberculous lymph nodules, but no active lesions were found. Active tuberculosis was evident only on the pleural surfaces. This tuberculous granulation tissue over the pleura was for the most part dense and rich in collagen (Figs. 3 and 4).



Fig. 5.—Heart and pericardium (hematoxylin and eosin stain, $\times 15$). Above is a broad zone of tuberculous granulation tissue in the pleura, in which there are pale round active tubercles. Next is a zone of normal extrapericardial fat. Then there is a dark zone made up of normal connective tissue of the epicardium. Between this and the normal epicardial fat there is a thin stratum of dense tuberculous granulation tissue, in which the pale round areas represent tubercles.

A similar, dense, collagenous, tuberculous granulation tissue filled the pericardial space (Fig. 5). Scattered through it were many active, proliferative tubercles. The epicardial fat was free from inflammation, and the coronary vessels were normal. The heart muscle was well preserved.

The hilar lymph nodes and the lymph node between the pericardium and trachea showed no evidence of active tuberculosis. These were all replaced almost entirely by dense cicatricial tissue (Fig. 6).

Sections of spleen and liver showed a few active, recently developed tubercles, but no other organs showed evidence of tuberculosis.

A section of skin from the region of the operation was free from evidence of inflammation. In the corium there was a moderate amount of recently extravasated blood.

The tuberculous process, even in the active tubercles, was predominantly proliferative in character. This proliferation of connective tissue and the elaboration of collagen resulted in a process in which cicatrization far overshadowed the sequences of inflammation. Using "cicatrix" in this sense, the autopsy observations can be summarized as follows: A thin, tough, continuous cicatrix covered the parietal and the visceral pleura, and the two were for the most part fused. A similar cicatrix bound parietal and visceral pericardium together, except anteriorly, where a true cicatrix bound the heart to the sternum. Finally, a tuberculous lymph node in which there was the same cicatrizing type of reaction bound the trachea to the pericardium.



Fig. 6.—This shows normal trachea with lymph node adherent. The lymph node is made up almost completely of dense cicatricial tissue. The dark islands are composed of lymphocytes and carbon particles. (Hematoxylin and eosin stain, $\times 15$.)

DISCUSSION

In approaching the problem of explaining the disability caused by these lesions two properties of cicatricial tissues may be recalled: resistance to stretching, and a strong tendency to contraction. The work

in recent years of Churchill,¹ Volhard and Schmieden,² White,³ Beck,⁴ Burwell and Blalock⁵ and others has served to show how such a pericardial scar may interfere with diastole. Though under these circumstances systole of the ventricle may be relatively unopposed, such interference with filling leads to a reduced stroke volume and an elevated venous pressure, with all their discomforts and dangers.

A similar limitation appears in this patient to have bound the lungs also. The normal mobility of the pleura permits expansion of the lungs during inspiration. The cicatrices which covered the whole area of visceral and parietal pleura opposed such expansion, reduced the volume of the lung at rest, and allowed only a minute and inadequate tidal volume from movement of the chest. The vital capacity fell from 3,100 to 600 c.c.

Finally, the trachea was fixed to the pericardium and the pericardium to the diaphragm. This limited further the descent of the diaphragm, and also interfered with the normal movement of the trachea during swallowing. Whether death was immediately due to cerebral edema or to some terminal cardiac disorder, such as ventricular fibrillation, it was, in either case, the result of asphyxia from mechanical interference with respiration.

This patient's course may also bring some evidence to bear on the troublesome question of whether pericardiectomy in a patient with active tuberculous pericarditis tends to "stir up" or to disseminate the infection. In this patient, it will be recalled that pleural friction rubs were heard on both sides of the chest, and that organisms were found in fluid from the left pleural cavity long before the operation. The real seat of trauma from the operation was the pericardium, yet there appeared to be no evidence of activation of the pericardial process. It appears, therefore, that the operation only relieved the mechanical obstruction to the entry of blood into the heart, and neither accelerated nor retarded the progress of the tuberculous infection.

SUMMARY

This patient had tuberculous pericarditis with cardiac constriction, plus bilateral tuberculous pleurisy. Pericardiectomy served to relieve the cardiac tamponade. He then developed an extreme limitation of his respiratory excursion, which apparently led to his death. Autopsy revealed an actively tuberculous constrictive thickening of the pericardium covering the heart, and a similar limiting structure completely encompassing the lungs.

There was an interesting parallelism between the effect of the pericardial lesion on the heart and that of the pleural lesion on the lung. Each interfered with the expansion and filling of an organ which must expand and fill to carry out its essential function. Because of this func-

tional similarity, it appears reasonable to apply to the pleural affection the term that is accepted as descriptive of the pericardial one. Hence, it is referred to as *constrictive pleuritis*.

REFERENCES

1. Churchill, E. D.: Decortication of the Heart (Delorme) for Adhesive Pericarditis, *Arch. Surg.* 19: 1457, 1929.
2. Volhard and Schmieden: Ueber Erkennung und Behandlung der Umklammerung des Herzens durch schwierige Perikarditis, *Klin. Wehnschr.* 2: 5, 1923.
3. White, P. D.: Chronic Constrictive Pericarditis (Pick's Disease) Treated by Pericardial Resection, *Lancet* 2: 539, 1935.
4. Beck, C. S.: Surgical Treatment of Pericardial Scar, *J. A. M. A.* 97: 824, 1931.
5. Burwell, C. S., and Blalock, A.: Chronic Constrictive Pericarditis. Physiologic and Pathologic Considerations, *J. A. M. A.* 110: 265, 1938.

Corrigendum

In the article by F. N. Wilson and F. D. Johnston, entitled "The Occurrence in Angina Pectoris of Electrocardiographic Changes Similar in Magnitude and in Kind to Those Produced by Myocardial Infarction," which appeared in the July, 1941, issue of the Journal, Fig. 5, on page 71, was printed upside down.

Department of Reviews and Abstracts

Selected Abstracts

Eckstein, R. W., Roberts, J. T., Gregg, D. E., and Wearn, J. T.: Observations on the Role of the Thebesian Veins and Luminal Vessels in the Right Ventricle. *Am. J. Physiol.* 132: 648, 1941.

The role of the thebesian veins and luminal vessels of the right ventricle was studied by injecting India ink or Berlin blue into the isolated right ventricle of the beating heart.

There was no gross or microscopic injection of the myocardium when right ventricular systolic pressure was below left ventricular systolic pressure.

Gross and microscopic myocardial injection occurred only when right ventricular systolic and diastolic pressures exceeded left ventricular systolic and diastolic pressures, respectively.

Therefore, in the normally beating heart myocardial nourishment does not occur through these channels from the right ventricle.

AUTHORS.

Neumann, C., Cohn, A. E., and Burch, G. E.: A Quantitative Method for the Measurement of the Rate of Water Loss From Small Areas, With Results for Finger Tip, Toe Tip and Postero-Superior Portion of the Pinna of Normal Resting Adults. *Am. J. Physiol.* 132: 748, 1941.

A method is described for measuring the rate of water loss from small surfaces. The method consists in passing dry oxygen through chambers covering the surfaces and then conducting the moisture-containing oxygen through cold aluminum coils. From the difference in weight of the coils before and after the passage of the oxygen, the amount of water lost is learned. The method is accurate to 2.6 per cent. This error can, however, reach 9 per cent when less than 6 mg. of water are measured, but such low values were not encountered.

The rate of the elimination of water was studied from the right index finger tip, right second toe tip and posterosuperior portion of the right pinna of fifteen white, normal, resting adult subjects. The mean rate of water loss was found to be 1.86 mg. per square centimeter per 15 minutes for the finger tips, 1.18 mg. for the toe tips, and 0.48 mg. for the pinnae. The rate of water loss in the toe tips was approximately two-thirds as rapid as in the finger tips, and the rate for the pinnae was only one-quarter as rapid as that for the finger tips.

AUTHORS.

Wiggers, C. J.: The Ineffectiveness of Vagal Stimulation on Ventricular Fibrillation in Dogs. *Am. J. Physiol.* 133: 634, 1941.

In numerous trials on seventy-eight dogs in which ventricular fibrillation was induced by various means and at various times during the course of an experiment, stimulation of the vagus nerves by strong faradic shocks and at different times after onset of fibrillation never restored normal coordinated beats nor produced convincing changes in the usual trend of the fibrillating process. Two corollaries fol-

low: 1, the method is obviously without value as a resuscitating agent; and 2, crucial proof that the vagus has any effect on the fibrillating or normally contracting dog's ventricle still remains to be produced.

AUTHOR.

Wégria, R., Moe, G. K., and Wiggers, C. J.: Comparison of the Vulnerable Periods and Fibrillation Thresholds of Normal and Idioventricular Beats. *Am. J. Physiol.* 133: 651, 1941.

Our results indicate 1, that even in fresh hearts the vulnerable period of premature beats is extended nearly to the end of the isometric relaxation process, but 2, that the fibrillation threshold is not significantly altered. The first demonstration supplies supplementary evidence in harmony with our conception of the induction of fibrillation following coronary occlusion (4). On the other hand, we cannot confirm our interpretation that weak, prolonged, direct currents induce fibrillation when opening of the current occurs during the vulnerable period of a premature systole which has a reduced threshold.

Our results are also interesting in crystallizing our conception as to the ultimate processes which underlie the initiation of fibrillation. An asynchronous offset of fractionate contractions, caused either by a slight delay in their onset or by variations in their durations, is, as King has emphasized, considered essential to any concept as to how fibrillation starts. Our results certainly fail to show that a greater degree of asynchronicity in termination of contractions in premature beats reduces the fibrillation threshold. The sensitivity to fibrillation, therefore, seems to depend rather on some inherent characteristic of cardiac muscle at the beginning of the relaxation of its ultimate units. This is supported by our observations that the period of vulnerability is extended in beats which arise from an ipsiventricular focus. That is not solely due to greater difference in the termination of fractionate contractions—as we had postulated—is indicated by the facts 1, that the degree of extension is too great, and 2, that a similar extension occurs in normally excited ventricles with impaired function.

AUTHORS.

Leary, T.: Symposium on Sudden Death. Syphilitic Aortitis as a Cause of Sudden Death. *New England J. Med.* 223: 789, 1940.

Syphilitic aortitis is associated with overstimulation of the essential aortic blood vascular system, the vasa vasorum. With the excessive growth of blood vessels, which penetrate through the media into the intima, there is an excessive growth of fibroblastic tissue, which thickens the intima and tends to narrow and occlude the portions of the coronary arteries lying within the aortic wall. Marked narrowing or occlusion of the ostia may result in sudden death, of coronary type, in the early stages of the disease.

In addition to widening of the commissures and rolling of the cusps, the association of atherosclerosis with late syphilitic aortitis tends to be followed by calcification and diffuse dilatation of the aorta, including the ring. Dilatation of the ring produces aortic insufficiency, which may be followed by sudden death, of coronary type, but usually leads to late progressive cardiac decompensation. Rupture of aneurysms is also a cause of sudden death, as is the production of local dissecting aneurysms in the lower ascending aorta, with rupture into the pericardium.

Experimental atherosclerosis in the rabbit following the feeding of cholesterol results in late diffuse dilatation of the aorta resembling that found in combined syphilitic aortitis and atherosclerosis in man.

AUTHOR.

Weiss, S.: Symposium on Sudden Death. Instantaneous "Physiologic" Death. New England J. Med. 223: 793, 1940.

In cases of sudden death, post-mortem examination frequently fails to explain the mechanism of death. In the majority of cases the underlying structural lesions are chronic, and lesions of the same type may be found in cases in which they do not contribute to the cause of death. In cases of instantaneous death fresh lesions responsible for death are often absent. In the causation of instantaneous death, a hyperirritable myocardium of anoxic or infectious origin and hyperactive reflexes singly or in combination play the most important roles. The functional capacity of the heart before death in these cases may be adequate or good. The determining factor in instantaneous death is often physiologic.

The general nature of syncope is discussed. Evidence favors the concept that instantaneous death is often a fatal syncope. Asystole of various types and ventricular fibrillation are the usual causes.

AUTHOR.

Moritz, A. R.: Symposium on Sudden Death. New England J. Med. 223: 798, 1940.

Although this discussion of the causes of sudden death is in no sense complete, it includes some of the more important diseases that commonly predispose to unexpected collapse and death. They do so for one of two principal reasons. The disease may render the circulatory system hyperirritable, so that a minor stimulus or stress causes the latter to fail, or the disease may be suddenly converted from a condition that is compatible with life into one that is incompatible.

From a medical standpoint the chief interest in sudden death lies in the fact that its occurrence is often unnecessarily premature. Death may be the result of an avoidable trespass on the physical or functional reserve of the diseased part. This is particularly true in cases of sudden death from heart failure. If the diseased condition were recognized so that the person so affected could be advised how to live within the limits of his diminished reserve, there would be less likelihood of the commission of fatal physical or emotional excesses.

For the protection of such a patient and of persons who might be injured by him, he should be advised against any undertaking in which his sudden collapse might lead to physical injury to himself or others. It is apparent that a person threatened with sudden loss of consciousness should not drive an automobile, operate a public conveyance, or otherwise engage in potentially dangerous undertakings.

From a medicolegal standpoint the subject of sudden death is of great importance. On the ability of the medical examiner to recognize the lesions responsible for sudden death from natural causes may depend whether an obscure death leads to a criminal indictment or to no charge, or whether or not it results in a civil action for indemnification. Thus, the difference between a verdict of murder and an acquittal may rest on post-mortem evidence. The difference between double and single indemnity in the settlement of insurance claims or the difference between full workmen's compensation and no compensation is likewise apt to be dependent on evidence obtained at autopsy.

The investigation of the causes of sudden death constitutes a problem of far-reaching medical and medicolegal significance.

AUTHOR.

Kaplan, L. G., and Katz, L. N.: The Characteristic Electrocardiograms in Left Ventricular Strain With and Without Axis Deviation. *Am. J. M. Sc.* 201: 676, 1941.

The electrocardiographic patterns seen in 178 instances (twenty-four necropsied) of left ventricular strain are described.

The characteristic development of the classical S-T-T complex in left ventricular strain is emphasized.

The classical types and intermediate forms are described and the natural evolution of these is presented.

Approximately 15 per cent of the total cases in the present series did not show any axis deviation and 62.5 per cent of these had the classical S-T-T deviation in Lead I. This latter type is called the concordant type of left ventricular strain. It formed 19 per cent of all the cases with characteristic S-T-T changes in Lead I.

It was not possible to correlate heart size and the type of electrocardiographic pattern in left ventricular strain.

Accompanying right ventricular strain, either as a late result of left ventricular or of an associated independent cause, and changes in the heart's position are the probable chief causes for lack of axis deviation in the concordant type of left ventricular strain.

The S-T-T deviation in left ventricular strain is attributable to a distance in the retreat of activity in the ventricles, in part due to the hypertrophy itself and in part secondary to coronary insufficiency.

The practical importance of recognizing the concordant type of electrocardiogram in left ventricular strain is emphasized.

AUTHORS.

Scherf, D., and Weissberg, J.: The Alterations of the T Waves Caused by a Change of Posture. *Am. J. M. Sc.* 201: 693, 1941.

The phenomenon of flattening or inversion of a formerly positive T wave in Lead III in the upright position was studied in thirty-five patients. This inversion increased during deep inspiration and decreased at the end of maximum expiration with upward pressure on the diaphragm.

These observations speak against the assumption that cardiac damage or anoxia of the heart muscle can be the factor responsible for the electrocardiographic alterations. They confirm the conception that the inversion of the T wave is due to a change in posture, and therefore a change in contact between the heart and the neighboring tissues.

AUTHORS.

Flaxman, N.: Atrioventricular Nodal Rhythm. *Am. J. M. Sc.* 201: 857, 1941.

Atrioventricular nodal rhythm is an infrequent cardiac conduction disturbance which can be diagnosed only with the aid of the electrocardiograph. Its importance rests chiefly on the two facts that it is due to a large variety of causes, both cardiac and extracardiac, and that it indicates depression of the normal pacemaker of the heart, the sinoauricular node.

Neither digitalis nor quinidine, nor any other special drug is indicated in treatment since nodal rhythm does not tend to persist after the cause has subsided or has been removed. Treatment, if possible, should be directed against the underlying cause,

AUTHOR.

Blackford, L. M., and Parker, F. P.: Pulmonary Stenosis With Bundle Branch Block: Report of a Case With Sound Tracings and Semiserial Studies of the Conduction Bundle. *Arch. Int. Med.* 67: 1107, 1941.

A case is presented of pulmonary stenosis with right bundle branch block occurring in a man who died at 23. Congenital pulmonary stenosis was diagnosed several years before his death, but the electrocardiogram was interpreted as evidence of a septal defect.

Sound tracings lend little support to the opinion that bundle branch block can be diagnosed with the stethoscope.

Histologic studies confirm the thesis that the cause of bundle branch block is often interference with the blood supply of the interventricular septum.

Paroxysms of tachycardia in cases of serious heart disease indicate a grave prognosis.

AUTHORS.

Bain, C. W. C.: Variable Ventricular Complexes in Heart Block, and Their Relation to Bilateral Bundle Branch Block. *Brit. Heart J.* 3: 75, 1941.

Four cases of A-V heart block with varying ventricular complexes have been observed. In two the A-V block was nearly always complete, although retrograde conduction occurred at times from ventricle to auricle; in the other two the A-V block varied. Analysis of the curves obtained suggests that bilateral bundle conduction defects were present in all of these cases. In three the evidence pointed to multiple centers of impulse formation, and these all died from Stokes-Adams disease; in one it was concluded that variable conduction was taking place down each branch from a single idio-ventricular center, and he has had no Stokes-Adams attacks.

Varying ventricular complexes in A-V heart block usually signify the presence of bilateral bundle conduction defects.

The impulses may arise from one or more places in the ventricles. Multiple foci of origin increase considerably the risk of Stokes-Adams attacks.

The duration of the QRS in bundle branch block is in part a measure of the speed of conduction in the relatively healthy branch; in bilateral bundle lesions the accepted minimum must always be exceeded. In those cases in which one branch is conducting normally, this minimum width may not exceed 0.11 sec.

Some forms of atypical right branch block may represent incomplete right branch block, the wide QRS being due to the presence of bilateral defects.

AUTHOR.

Barber, H., and Osborn, G. R.: A Fatal Case of Myocardial Contusion. *Brit. Heart J.* 3: 127, 1941.

A fatal case of contusion of the myocardium has been described: there was no rupture of the heart muscle. The morbid anatomy has been compared with other records.

Reference is made to clinical histories, already published from this hospital, suggestive of recovery from contusion of the myocardium.

AUTHORS.

Wechsler, H. F., Farmer, L., and Urban, J. A.: A Case of Insulin Allergy Simulating Coronary Occlusion. *J. Lab. and Clin. Med.* 26: 1090, 1941.

The sodium ion depresses the blood sugar level in rabbits. In juvenile diabetic patients the administration of sodium salts decreases both blood sugar level and glycosuria. The mechanism of this action is unknown.

Potassium salts increased the blood sugar concentration and glycosuria of juvenile diabetic persons. This effect appears to be due to a stimulating effect on adrenalin discharge and is inhibited by magnesium.

There is no unanimity of opinion concerning the effect of calcium on the glycemic levels of various experimental animals. Calcium salts appear to depress the hyperglycemic effect of epinephrine in animals.

Nickel and cobalt salts, when added to insulin, delay the effect of the latter in normal rabbits and dogs, but not in diabetic human beings. Nickel and cobalt salts, when given alone, have no effect on blood sugar level of man or animals.

Zinc-deficient diet delays the absorption of carbohydrate from the gastrointestinal tract of rats. Zinc oxide has been found to produce glycosuria in dogs and pancreatic fibrosis in cats. The zinc content of the pancreases of diabetic persons is greatly below normal.

Zinc, aluminum, ferric chloride, nickel, or cobalt, when mixed with insulin, delays the action of the latter; calcium, magnesium, and potassium alum do not delay the effect of insulin when mixed with it.

Lead and manganese decrease the fasting blood sugar levels.

Phospho-24-tungstic acid, phosphomolybdic acid, molybdic acid, silico-tungstic acid, sodium tungstate, and ammonium phospho-18-tungstate appear to cause a decrease in blood sugar of diabetic persons.

Glycosuria has been observed after the administration of mercury, uranium, and chromium.

The administration of copper salts, both in man and animals, causes a decrease in the ability of adrenalin to mobilize liver glycogen.

AUTHORS.

White, P. D., and Bland, E. F.: Mitral Stenosis After Eighty. *J. A. M. A.* 116: 2001, 1941.

Four patients with mitral stenosis of moderate degree, proved at autopsy, survived the age of 80 years, two men aged 83 and 81, and two women aged 82 and 83. The first patient of the group, unaware of his heart trouble, carried on an active and eminently useful medical career, was a leader of his generation, and himself wrote on the good prognosis of many cases of rheumatic heart disease.

AUTHORS.

Cossio, P., Berconsky, I., and Gamba, R.: Pulmonary Stenosis and Nodular Ossification of the Lungs. *Rev. argen. de cardio.* 7: 385, 1941.

A case is described of cor pulmonale of subchronic evolution with multiple nodular ossification of the lungs verified at autopsy.

The nodular ossification of the lungs was due to a process of metaplasia of the connective tissue caused by a bronchioalveolar and arteriolar chronic inflammatory state. It is believed that the excess of work of the right ventricle was a consequence of the diminished diameter of the pulmonary arterioles.

The electrocardiographic alterations observed (deep S I and S II, negative T III and T IV) are believed to be due to disturbances in the metabolism of the heart muscle as a result of fatigue of the strained right ventricle, and not to a pulmonary coronary reflex.

Cor pulmonale and multiple nodular ossification of the lungs should be considered in the diagnosis whenever multiple nodular micronodular shadows are radiologically verified in the lungs accompanied by cardiac disturbances and the described electrocardiographic alterations.

AUTHORS.

Hubbard, J. P.: Paroxysmal Tachycardia and Its Treatment in Young Infants. *Am. J. Dis. Child.* 61: 687, 1941.

Nine cases of paroxysmal tachycardia occurring in young infants are reviewed. The fact that six of these were observed during one year stands in contrast to the sparsity of well-established cases in the literature and indicates that such cases may occur more often in the early months of life than has heretofore been recognized.

In these nine cases and in nineteen collected from the literature, in all of which the infants were less than 1 year old, there is a distinctive clinical course which in certain respects differs from that in cases of paroxysmal tachycardia in older children or in adults. The heart rate is usually 250 to 300, and if the tachycardia continues for several days, as it is likely to do, it brings on circulatory failure, which is associated with vomiting, dyspnea, fever, leucocytosis, cardiac enlargement, pulmonary possibility and engorgement of the liver. Failure to bear in mind the possibility that paroxysmal tachycardia is present in a young infant may lead to such misdiagnoses as pneumonia or congenital idiopathic hypertrophy of the heart. Paroxysmal tachycardia in young infants may be severe and may have a fatal termination if untreated, but so far as present experience indicates, the disease responds satisfactorily to adequate doses of digitalis.

AUTHOR.

Kuttner, A. G., and Krumwiede, E.: Observations on the Effect of Streptococcal Upper Respiratory Infections on Rheumatic Children: A Three-Year Study. *J. Clin. Investigation* 20: 273, 1941.

The effects of three outbreaks of streptococcal upper respiratory infections during three successive winters in a colony of rheumatic children are described. Each of these outbreaks was due to infections with a single type of Group A beta hemolytic streptococci, but during each epidemic a different type was prevalent.

The incidence of rheumatic recurrences following these streptococcal upper respiratory infections varied greatly—from none to a large proportion of the cases.

A comparison of the epidemic strains failed to reveal any significant differences which might account for the variations in the incidence of rheumatic recurrences.

A comparison of the rheumatic histories of children who escaped and of those who developed rheumatic recurrences following pharyngitis due to "effective" strains of streptococci likewise did not show any striking differences. Our findings suggest that the vulnerability of the rheumatic subject to the effect of streptococcal upper respiratory infections is variable, and depends on factors which at the present time are not understood.

No rheumatic recurrences were observed in children who escaped streptococcal upper respiratory infections during the three-year period.

AUTHORS.

Reyersbach, G., Lenert, T. F., and Kuttner, A. G.: An Epidemic of Influenza B Occurring in a Group of Rheumatic Children Concurrent With an Outbreak of Streptococcal Pharyngitis; Clinical and Epidemiological Observations. *J. Clin. Investigation* 20: 289, 1941.

An outbreak of influenza due to a recently described influenza virus, Influenza B (2), in a relatively isolated group of rheumatic children has been described.

The clinical symptoms were mild and remained remarkably uniform throughout the epidemic. No complications of any kind developed.

The characteristic laboratory finding was a relative leucopenia.

No evidence was obtained to suggest that the virulence of a Group A *Beta hemolytic streptococcus* of proved pathogenicity was increased by this strain of influenza virus.

Rheumatic recurrences were not precipitated by the influenza outbreak.

AUTHORS.

Walsh, B. J., and Sprague, H. B.: Character of Congestive Failure in Children With Active Rheumatic Fever. *Am. J. Dis. Child.* 61: 1003, 1941.

The clinical features of congestive failure in children with rheumatic heart disease are described, the observations being based on a study of forty-four children between the ages of 3 and 15 years who were seen between July 1, 1937, and April 1, 1940, at the House of the Good Samaritan.

The initial signs of heart failure in these forty-four children with rheumatic fever and congestive failure were enlargement of the liver and puffiness of the face accompanied by unexpected gain in weight. A few children with congestive failure and active rheumatic fever preferred to lie flat in bed. These children had marked puffiness of the face, which caused them to look as if they had primary renal disease.

Pulmonary râles were seldom heard in these children, their appearance being limited to the terminal stages of the illness.

Other important evidences of congestive failure in children with rheumatic fever and congestive failure were high venous pressure apparent at the onset of the failure, a shift of the electrical axis of the heart to the right, which increased with progression of the heart failure and decreased or disappeared with the patient's improvement or recovery, and a well-marked diastolic gallop rhythm along the upper left sternal border.

AUTHORS.

Corbit, J. D., Jr.: The Effect of Pregnancy Upon Experimental Hypertension in the Rabbit. *Am. J. M. Sc.* 201: 876, 1941.

A study was made of the fluctuations in: a, blood pressure; b, blood urea; and c, in the excretion of urinary protein during pregnancy in normal rabbits, and in rabbits in which arterial tension was previously raised by the experimental induction of renal ischemia.

It was found in both groups of animals that pregnancy tended to bring about a lowering of the systolic pressure a few days before the onset of labor. The extent of this fall amounted to about 20 per cent of the pre-pregnancy tension. The return of pressure to the pre-pregnancy level occurred gradually during the first two to three weeks post partum.

In the normal animal these fluctuations of arterial tension were not accompanied by significant alterations of blood urea, nor by proteinuria. In the renal ischemic animals, however, there was a coincidental, slight, prepartal fall of blood urea, and a tendency to proteinuria. In no animal was there evidence to indicate that these changes were due to ill health. The normal gestational increase of maternal body weight took place, the pregnancies were normal in duration, and the number of pups born was normal for this species.

The extent of the prepartal fall of blood pressure was proportionate to the number of fetuses present.

AUTHOR.

Garreton-Silva, A., Croxatto, R., Fuenzalida, O., and Viveros, R.: Experimental Investigation of Pressor Substance With Blood of Patients With Arterial Hypertension. *Rev. argent de cardiol.* 8: 1, 1941.

Citrated plasma from human arterial or venous blood was perfused through a L wen-Trendelenburg preparation using the Chilean frog.

The plasma from twenty-eight adult patients with different types of hypertension, when mixed with Page's renin activator (hypertensin precursor) produced in all cases a vasoconstrictor action. Hypertensive plasma or activator was inactive when perfused alone and normal plasma alone or mixed with the activator, showed also no vasoconstrictor action.

The presence of vasoconstrictor substances related to renin (angiotonin or hypertensin) in the blood of hypertensive subjects seems to indicate that Goldblatt's phenomenon (renal ischemia) plays a role in the pathogenesis of those cases.

AUTHORS.

Riggs, Theodore F., and Satterthwaite, Richard W.: Unilateral Kidney With Partial Occlusion of the Renal Artery Associated With Hypertension: Case Report. *J. Urology* 45: 513, 1941.

An unusual anomaly of a single kidney and ureter on the right side, with obstruction of the renal artery by a small dissecting aneurysm and a localized sclerotic plaque, is reported.

The development of hypertension in its acute phase in this case may have been initiated by the partial occlusion of the lumen of the main renal artery and its three branches by this aneurysm.

Cases of hypertension, especially those of sudden onset, no matter what the age of the patient, would appear to warrant complete investigation of the renal arteries for abnormalities.

AUTHORS.

Johnson, Carl A.: A Study of the Clinical Manifestations and the Results of Treatment of Twenty-Two Patients With Raynaud's Symptoms. *Surg. Gynec. & Obst.* 72: 889, 1941.

The results of a study of twenty-two patients with Raynaud's syndrome are presented with the following opinions:

1. Observations on this series of patients confirm Hutchinson's statement made more than fifty years ago that what is known as Raynaud's disease is not a clinical entity, and that the peripheral manifestations observed are merely symptoms of some more fundamental disease.

2. The vascular changes during a Raynaud's attack are not necessarily due to an active vascular constriction, but may be the results of a vasodilatation in the palmar arch with a diversion of blood from the fingers and a passive collapse of the vessels.

3. In this series of patients, surgery of the sympathetic nervous system was a therapeutic failure but medical management gave considerable relief in a number of patients.

AUTHOR.

Hussey, H. H., and Katz, S.: The Comparative Value of Ether and Paraldehyde as Agents for Measurement of the Arm to Lung Circulation Time in Fifty Patients With, and Fifty Patients Without Heart Failure. *Am. J. M. Sc.* 201: 669, 1941.

Measurement of the circulation time is useful in the diagnosis and study of a number of diseases, and especially of heart failure.

A comparison of the relative value of ether and paraldehyde for measurement of the arm-to-lung circulation time is presented. These two drugs have already been reported to give approximately equal results in normal persons. This has been confirmed in our studies in fifty patients having no cause for delay of the circulation time.

Comparison of circulation time measurements obtained almost simultaneously by means of ether and paraldehyde in each of fifty patients with heart failure shows that measurements with paraldehyde are usually significantly longer than those with ether. Such differences constitute an inaccuracy which may be misleading clinically.

Speculation as to the possible reasons for the discrepancy in measurements made with ether and paraldehyde is offered, and the conclusion drawn that ether is the agent of choice for estimation of the arm-to-lung circulation time.

AUTHORS.

Bedford, D. E., and Lovibond, J. L.: Hydrothorax in Heart Failure. *Brit. Heart J.* 3: 93, 1941.

Old and recent views on hydrothorax have been reviewed and its clinical and radiologic diagnoses have been discussed.

Hydrothorax was observed at some stage in 136 (38.5 per cent) of 356 cases of congestive heart failure, diagnosis being mostly radiologic, and in 45 (41.3 per cent) of 109 cases of failure examined post mortem. The hydrothorax was right-sided in sixty-eight cases, left-sided in forty-two, and bilateral in twenty-six; this included eleven interlobar effusions. Neither these nor previous statistics show right unilateral hydrothorax to be as predominant as generally supposed.

A definite relation was found between the site of the hydrothorax and the underlying heart condition. Hypertension, left heart failure, and normal rhythm favored a left hydrothorax; mitral stenosis, combined right and left heart failure, and auricular fibrillation favored a right hydrothorax. Clinical hydrothorax, which clears up rapidly with treatment, can rarely be attributed to pulmonary infarction, but in the terminal stages of heart failure and at post mortem examination infarction is often an associated condition.

Hydrothorax is not uncommon in left heart failure, when it is a complication of pulmonary congestion. This explains its occurrence without edema. In pure right heart failure ascites without hydrothorax is the rule.

The pleural fluid in hydrothorax may show some degree of inflammatory reaction, probably due to its contact with chronically congested lungs, and no sharp division between transudate and exudate (cardiac pleurisy) can usually be made.

In response to treatment by mercurial diuretics, hydrothorax often clears up completely within a few weeks or months, leaving no residue; but occasionally it becomes chronic and persists for a year or longer.

The pathogenesis of hydrothorax has been discussed and reasons given for regarding it as related to pulmonary rather than systemic venous engorgement, and as a transudate from the visceral rather than the parietal pleura. Unilateral and interlobar hydrothorax can better be explained in terms of pulmonary than of systemic stasis.

AUTHORS.

Sauer, P. K.: The Choice of Anesthesia in Operative Patients With Heart Disease. *Am. J. Surg.* 48: 532, 1940.

The most common types of heart disease have been discussed from the standpoint of a choice of anesthetics.

Anesthetics have been chosen for each type of heart disease that will involve the least risk.

Contraindications to certain anesthetics in various types of heart disease have been emphasized.

A suggestion for the improvement of the service by a more careful consideration in the choice of anesthetics by both the surgeon and the anesthetist has been made.

AUTHOR.

Wood, P.: Da Costa's Syndrome (or Effort Syndrome) (Goulstonian Lectures to the Royal College of Physicians of London, 1941). British Med. J. 1: 767, 1941.

The symptoms and signs of Da Costa's syndrome more closely resemble those of emotion, especially fear, than those of effort in the normal subject.

The mechanism of the somatic manifestations depends upon central stimulation, not upon hypersensitivity of the peripheral autonomic gear.

This central stimulus is emotional, and is commonly the result of fear.

The reaction becomes linked to effort by a variety of devices, which include misinterpretation of emotional symptoms, certain vicious circular patterns, the growth of a conviction that the heart is to blame, consequent fear of sudden death on exertion, conditioning, and hysteria.

Incapacity tends to be exaggerated consciously or subconsciously in order to protect the individual from further painful emotional experience.

Treatment in the Army is shackled by inability to remove the distressing environmental factors which have caused or have aggravated the breakdown; by the difficulty in establishing intimate contact with a patient who did not choose his medical confidant; by the duty of having to serve the State first, the patient second.

It is urged that the diagnosis of "effort syndrome" be dropped. A proper psychiatric diagnosis is nearly always available; if attention is to be called to the presence of effort intolerance, let effort intolerance be added in brackets.

AUTHOR.

Lichtman, S. S., and Bierman, William: The Treatment of Subacute Bacterial Endocarditis. J. A. M. A. 116: 286, 1941.

Among 200 cases of subacute bacterial endocarditis due to *Streptococcus viridans* and nonhemolyticus collected from the literature and the records of the Mount Sinai Hospital in which the sulfonamide drugs were administered, recovery occurred in twelve, an incidence of 6 per cent recovery.

Among forty-three patients treated with combined chemotherapy and heparin, five recovered, an incidence of 11.5 per cent recovery.

Among twenty-four patients treated by chemotherapy and physically induced hyperthermia, four recovered, an incidence of 16 per cent recovery. Of twenty-one patients treated by chemotherapy and hyperthermia induced by intravenous typhoid-paratyphoid vaccine, five recovered, an incidence of 25 per cent recovery.

The number of cases in the three series treated by combined methods is still too small to yield an accurate statistical estimate of the incidence of recovery in each group. This preliminary review of the results obtained thus far is encouraging. The combined methods of therapy seem to promise a greater incidence of recovery than may be anticipated in the natural course of the disease or after treatment with the sulfonamide drugs alone.

AUTHORS.

Book Review

CLINICAL ASPECTS OF THE ELECTROCARDIOGRAM: By Harold E. B. Pardee, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College, Ed. 4, 434 pages, 102 figures, Paul B. Hoeber, Inc., New York and London, 1941, \$5.75.

The first edition of this deservedly popular book, which was published in 1924, was quickly recognized as one of the best texts on clinical electrocardiography. As each successive edition appeared, this reviewer has always included it among the books recommended to those who desired more than a bowing acquaintance with the subject. The present edition has been revised and brought up to date. It maintains the high standard of the previous editions.

Since the author has grown up, as it were, with his subject, and has been an outstanding investigator, clinician, and teacher for over twenty years, he is eminently qualified for his task. In dealing with a literature so voluminous as that of clinical electrocardiography, the selection of material for a book of this kind becomes a matter of major importance. This has been done with discriminating judgment.

Among the excellent features is the chapter entitled "The Normal Electrocardiogram," which covers forty-four pages. Careful study of this chapter and the one entitled "Hypertrophy of the Chambers of the Heart" will prove particularly helpful to those who wish to learn how to interpret electrocardiograms.

The author remains a convinced adherent of the Einthoven equilateral triangle hypothesis and accounts for all electrocardiographic deflections in limb leads on this basis. In his discussion of the theory of the electrocardiogram one obtains no inkling of the fact that there are dissenters from the faith in Einthoven's famous group of assumptions. Even Eyster's fundamentally important contribution, "The Nature of the Electrical Field Around the Heart," which has done much to impair the prestige of the triangle hypothesis, is not mentioned in this connection. This is to be regretted, for the attacks made during the past few years on the validity of the assumptions which underlie the hypothesis cannot be ignored much longer. However, no fair-minded person would criticize the author for his adherence to a view which has not only survived for nearly thirty years, but is still venerated by the majority of workers and taught in practically all textbooks.

It is a pleasure to welcome and recommend this new edition of a carefully prepared book which will doubtless continue to serve a very useful function as an introduction to clinical electrocardiography.

CHARLES C. WOLFERTH.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. PAUL D. WHITE
President
DR. ROY W. SCOTT
Vice-President

DR. T. HOMER COFFEN
Treasurer
DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

*DR. EDGAR V. ALLEN	Rochester, Minn.	*DR. EDWIN P. MAYNARD, JR.	Brooklyn
DR. T. HOMER COFFEN	Portland, Ore.	*DR. THOMAS M. McMILLAN	Philadelphia
DR. CLARENCE DE LA CHAPELLE	New York City	DR. JONATHAN MEAKINS	Montreal
DR. WILLIAM DOCK	San Francisco	DR. E. STERLING NICHOL	Miami
DR. HUGH FARRIS, St. John, N. B., Canada		DR. FRANKLIN R. NUZUM	Santa Barbara
DR. NORMAN E. FREEMAN	Philadelphia	*DR. STEWART R. ROBERTS	Atlanta
DR. GEORGE R. HERRMANN	Galveston	*DR. ROY W. SCOTT	Cleveland
DR. T. DUCKETT JONES	Boston	DR. FRED M. SMITH	Iowa City
*DR. WILLIAM J. KERR	San Francisco	*DR. HOWARD B. SPRAGUE	Boston
DR. EMANUEL LIBMAN	New York City	DR. WILLIAM D. STROUD	Philadelphia
DR. DREW LUTEN	St. Louis	*DR. PAUL D. WHITE	Boston
DR. GILBERT MARQUARDT	Chicago	DR. FRANK N. WILSON	Ann Arbor
*DR. H. M. MARVIN	New Haven	*DR. IRVING S. WRIGHT	New York City
		DR. WALLACE M. YATER	Washington, D. C.

DR. H. M. MARVIN, *Chairman, Executive Committee
and Acting Executive Secretary*

GERTRUDE P. WOOD, *Office Secretary*

TELEPHONE CIRCLE 5-8000

THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-seven physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$11.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

•Executive Committee.

The American Heart Journal

VOL. 22

SEPTEMBER, 1941

No. 3

Original Communications

THE AUTONOMIC MECHANISM OF HEAT CONSERVATION AND DISSIPATION

I. EFFECTS OF HEATING THE BODY

EVIDENCE FOR THE EXISTENCE OF CAPILLARY DILATOR NERVES IN ANTERIOR ROOTS

OLAN R. HYNDMAN, M.D., AND JULIUS WOLKIN, M.D.
IOWA CITY, IOWA

AMONG the important functions of the skin are the conservation and dissipation of heat for the purpose of maintaining a constant central temperature. The thoracolumbar or sympathetic* division of the autonomic nervous system plays a major role in subserving this function. Much can be learned concerning this function of the sympathetic system by studying the skin reactions of patients who have had various operative procedures performed on the nervous system (particularly sympathetic). We have studied the effects of heat, cold, adrenaline, and pilocarpine on a series of such patients. We have studied the effect of heat on a larger series than that reported here, but this group is representative.

Our studies have involved observations concerning three factors in heat regulation by the skin: sudomotor, vasomotor, and pilomotor. There is evidence that responses may occur in each of these systems and be governed by (1) the end organ itself (sweat gland, arteriole and capillary, and pilomotor muscle), (2) by a reflex through the spinal cord, and (3) by central (hypothalamic) control. For convenience we will hereinafter refer to these three mechanisms as first, second, and third order reactions, respectively.

Sweat Gland.—We have presented evidence¹ that the sweat gland itself may respond to a heat stimulus after its nerve fiber has degenerated, if the skin is covered.

From the Department of Surgery, Neurosurgical Service, College of Medicine, State University of Iowa.

Received for publication Nov. 14, 1940.

*Sympathetic is used in contradistinction to the parasympathetic (craniosacral) division.

Reflex sweating (second order reaction) after complete transverse lesions of the cord² and thermoregulatory sweating (third order reaction)³ are well-known phenomena.

Vasomotor System of Skin.—One must give separate consideration to capillaries and arterioles. The first order mechanism is easily demonstrated in patients after postganglionic degeneration by placing them in hot or cold environments or by placing hot or cold objects on the sympathectomized part.

We have not been successful in demonstrating the second order vasomotor reaction convincingly, but it probably functions to some degree. We feel that the tests should be carried out on spinal patients or spinal animals.⁴ On one spinal patient we were able to elicit no significant contralateral changes in the skin temperature of the toes when the opposite extremity was immersed in cold water at a time when the cord reflexes were intact. Gibbon and Landis⁵ found that, when the forearms of normal persons in a cool room were immersed in warm water, the temperature of the toes would rise considerably. This, however, is most likely a third order mechanism, and not reflex to any great extent through the cord. They also gave evidence to verify this reasoning.

That there is a third order (hypothalamic) vasomotor control of arterioles is well known.⁶ We are adding to this strong evidence that capillary dilatation is centrally controlled.

Pilomotor System.—We have always been able to elicit a local pilomotor response to pinching in sympathectomized skin areas. Pilomotor activity en masse in spinal man and third order or centrally controlled pilomotor activity are known to exist.⁶ Our studies would indicate that the first and third order mechanisms are by far the most important and that the reflex mechanism through the cord normally plays a very minor role.

No true parasympathetic (craniosacral) fibers innervating the sweat glands, arterioles, or pilomotor muscles of the skin have been demonstrated. These structures are controlled by the thoracolumbar or sympathetic division only. However, many investigators have demonstrated that there are two types of fibers in the sympathetic system, and it is now generally accepted that two types do exist, namely, cholinergic and adrenergic.⁷⁻¹² It does not seem possible that one type of fiber could subserve all the functions which are known to take place in the skin structures, nor can it be assumed that the dual function ascribed to the peripheral activity of hormones can exist without postulating a dual innervation. For example, there is evidence for the existence of vasodilator as well as vasoconstrictor fibers to the arterioles of the skin. Our study does not prove or disprove that there are vasodilator fibers to arterioles, but Lewis and Pickering,¹³ by ingenious experiments, have produced evidence that they exist. Also, there is some evidence that, when cholinergic fibers are active, the adrenergic ones are inhibited, and vice versa. For example, in postoperative hyperthermia, which,

we believe, is a manifestation of extreme overactivity of the heat-conserving mechanism, we have observed marked vasoconstriction, waves of pilomotor activity, and absence of sweating. In such a case it has been very difficult, if not impossible, to break through the sweat "inhibition" with pilocarpine. Lastly, it might be assumed that adrenaline would inhibit sweating. Although we have not tested this, Higier⁷ regards it as proved.

The efficiency with which the skin may conserve or dissipate heat in man is quite remarkable. In hyperthermia the skin may be icy cold when the circulating blood has a temperature of 108° F.

We should like to emphasize that in this, as in other studies involving neurophysiology, normal reactions are functionally integrated toward a purposeful end. The third order, or centrally controlled mechanism, is dominant. The general location of primary heat-conserving and heat-dissipating centers in the hypothalamus⁶ is known,¹⁴ and this head ganglion responds to the needs of the organism. So far as the thermoregulatory control is concerned, the response is standard. In heat conservation there are vasoconstriction, pilomotor activity, and absence of sweating. In heat dissipation there is vasodilatation of the arterioles of the skin, followed, when the need is extreme, by capillary dilatation, sweating, and absence of pilomotor activity. The higher centers, i.e., the frontal lobes, impel the hypothalamus under certain conditions to produce skin reactions which do not follow the usual pattern of thermoregulatory activity. The combination of vasoconstriction and sweating which occurs with fear and emotional blushing are examples of such a reaction.

It does not follow that, because a certain stimulus causes vasoconstriction in the skin, it will also cause vasoconstriction in the deeper vessels. The reverse may be true, but in any case the responses will depend upon the biologic objective. Talbot¹⁵ has made some very extensive studies of skin temperature under varying conditions. He found that during exercise there is a fall in skin temperature, even though there is a rise in body temperature. In this case heat elimination does not keep pace with heat production. During the half hour after activity has ceased, the skin temperature rises frequently to a point much higher than that which preceded exercise. Benedict and Parmenter¹⁶ also found a lowering of skin temperature during exercise. These results can be explained partly by vasoconstriction in the skin to mobilize blood where it is most needed.

Again, the responses obtained when an anterior spinal root is artificially stimulated are vasoconstriction, pilomotor reaction, and sweating,¹⁷ i.e., a heterogeneous, purposeless combination which should not be accepted as indicating integration of function.

Of the three thermoregulatory responses in man, sweating and vasomotor control are the most important; the pilomotor reaction is only a

vestige of an important function in animals and birds. Sweat can serve its purpose of having a cooling effect only in proportion to evaporation. If the latter cannot occur, sweating must surely be of little value in dissipating heat. Vasodilatation is undoubtedly the most important factor in heat dissipation in man.

Although skin temperature may be accepted as a reasonably accurate index of the rate of heat dissipation, this is true only within certain limits. Heat may be dissipated in two ways by vasodilatation. The arterioles may open, thereby increasing the minute volume flow of blood subject to radiation. In this case, and from a purely physical standpoint, skin temperature would approach the central temperature as a limit. Actually, in our experience, it has never reached the central temperature. If the arterioles are in a state of maximal dilatation, numerous capillaries may open, which would increase the amount of blood exposed to radiation, and reduce its velocity. Under these conditions the skin temperature will no longer be an index to the rate of heat dissipation. Indeed, it is conceivable that the skin may become colder even when the rate of heat dissipation has increased. When the capillary bed opens up, the skin presents a sunburn flush, but its temperature does not always exceed that of an unflushed zone. Although capillary and arteriolar dilatation probably occur to some degree concomitantly, we have seldom seen visible evidence of flushing unless the need for heat dissipation was great.

The criticism might be offered that the skin may act as an inanimate body under the conditions of these experiments. We feel, however, that the presence of circulating blood in the skin clearly dispels this criticism. In fact, the temperature of the skin is at all times a function of the temperature of the blood and of the factors which control its rate of flow. To obtain data relevant to this problem was the exact purpose of these experiments. The cabinet was always twenty or more degrees warmer than the body of the patient, and yet the skin temperature never at any time rose as high as the body temperature because the skin does not respond as an inanimate body.

It might also be supposed that sweating would interfere with the results. Some of the experiments were done with the subject under the influence of atropine, and others without atropine. When atropine was used, in some cases the skin remained thoroughly dry throughout the experiment, but, in any case, the results were always the same with or without sweating—that is, in patients who had had a unilateral sympathectomy the temperature of the fingers or toes was the same on both sides at the end of the experiment. We feel that this fact in itself bears out our contention that sweat has little or no influence on the temperature of the skin except through the cooling effect of evaporation. Under the conditions of these experiments the chance for evaporation was absent or minimal.

METHOD

Skin temperatures were taken with a Tycos Dermatherm.* Basal readings were made shortly before placing the patient in the cabinet. The patient was exposed for twenty to thirty minutes at a constant room temperature before the basal readings were taken. He was then placed on his back in a Burdick fever therapy cabinet† which had attained a maximum temperature with dry heat. The patient's head remained outside the cabinet. At the termination of the experiment, which lasted forty-five minutes to an hour, the cabinet was opened and the skin temperatures taken. The mouth temperature, pulse rate, and blood pressure were followed. The thermometer of the dermatherm was checked for each set of readings, and the absolute temperature of the skin was calculated in degrees centigrade.

We studied the effect of external heat, the inductotherm, and the inductotherm after a hypodermic injection of atropine (gr. $\frac{1}{75}$) to prevent sweating and to encourage the most marked vasomotor reactions. The inductotherm plus atropine produced the most marked and interesting responses.

EFFECTS OF HEATING THE BODY

Experiment 1.—Nov. 24, 1939. Effect of dry heat. Ralph McG., aged 55 years, one hundred twenty days after the removal of the left inferior cervical and the upper six dorsal ganglia (Table I).

TABLE I
EFFECT OF HIGH TEMPERATURE ON SKIN

PART	SKIN TEMPERATURE (°C)						
	RIGHT	LEFT		RIGHT	LEFT	RIGHT*	LEFT*
Forehead	31.6	31.6		31.7	32.7	+0.1	+1.1
Cheek	31.1	31.1		34.7	32.7	+3.6	+1.6
Neck	32.1	32.6		32.2	33.2	+0.1	+0.6
Chest	32.1	32.1		32.2	34.2	+1.1	+2.1
Arm	31.6	31.6		32.7	33.7	+1.1	+2.1
Forearm	31.6	32.1		32.7	33.7	+1.1	+1.6
Finger	31.6	32.1		32.7	32.7	+1.1	+0.6
Abdomen	33.1	33.1		32.7	32.7	-0.4	-0.4
Thigh	32.1	32.1		32.2	32.2	+0.1	+0.1
Calf	32.1	32.1		32.2	32.2	+0.1	+0.1
Ankle	31.6	31.1		32.2	32.2	+0.6	+1.1
Mouth temperature	36.77° C. 98.2° F.			36.88° C. 98.4° F.			
B. P.	114/70			96/64			
Pulse	96			104			
Time (P.M.)	2:26		2:30	3:20			
Remarks	Basal		In cabinet	Cabinet opened			

Observations: There was good sweating over the body except in the sympathetomized zone. No flushing of the skin was seen.

*Differences between first and last readings.

Room temperature, 26.7° C.; temperature of cabinet, 45.0° C. (dry heat).

Comment.—The left middle finger was only 0.5° C. warmer than the right at the beginning.‡ The temperatures of the two were equal at the end of the experiment; they had become only slightly warmer. The mouth temperature rose only 0.2° F.

Experiment 2.—Dec. 4, 1939. Effect of dry heat and atropine. Ralph McG., 130 days after operation. (Table II.)

*Taylor Instrument Company, Rochester, N. Y.

†We wish to thank the members of the Department of Medicine for allowing us to use the Burdick cabinets, and Miss Genevieve Wendlandt for her helpful cooperation in carrying out the experiments.

‡The difference in the temperatures of the fingers on the two sides was no greater than this after the operation.

Comment.—The temperatures of the middle fingers were equal at the beginning and end of the experiment; they rose 3.7° C. On the whole, the temperatures rose higher than in the previous experiment, and the mouth temperature rose 1° F. The demarcation of flushing on the face, as noted below Table II, was marked.

TABLE II
EFFECT OF HIGH TEMPERATURE AND ATROPINE ON SKIN

PART	SKIN TEMPERATURE (°C)						
	RIGHT	LEFT		RIGHT	LEFT	RIGHT*	LEFT*
Forehead	32.5	32.5		32.7	32.7	+0.2	+0.2
Cheek	32.5	32.5		33.2	31.7	+0.7	-0.8
Neck	31.5	31.5		32.7	32.2	+1.2	+0.7
Chest	33.0	33.0		34.2	35.2	+1.2	+2.2
Arm	33.0	33.0		34.2	34.7	+1.2	+1.7
Forearm	32.5	32.5		33.7	34.2	+1.2	+1.7
Finger	31.5	31.5		35.2	35.2	+3.7	+3.7
Abdomen	33.0	33.0		34.2	34.2	+1.2	+1.2
Thigh	32.0	32.5		34.2	34.2	+2.2	+1.7
Calf	32.0	32.0		34.2	34.7	+2.2	+2.7
Ankle	32.0	31.5		34.7	34.7	+2.7	+3.2
Mouth temperature	36.66° C. 98.0° F.			37.22° C. 99.0° F.			
B. P.	90/64			92/66			
Pulse	96			120			
Time (P.M.)	3:15		3:18	4:15			
Remarks	Basal Atropine (gr. $\frac{1}{15}$) ^H		In cabinet	Cabinet opened			

Observations.—There were complete absence of sweating, marked flushing on the normal side of the face and on the normal ear and no flushing on the face and ear of the denervated side. The line of demarcation was sharp and definite.

*Differences between first and last readings.

Room temperature, 27.7° C.; temperature of cabinet, 45.0° C. (dry heat).

TABLE III
EFFECT OF INDUCTOTHERM ON SKIN

PART	SKIN TEMPERATURE (°C)						
	RIGHT	LEFT		RIGHT	LEFT	RIGHT*	LEFT*
Forehead	31.5	31.5		33.4	32.9	+1.9	+1.4
Cheek	31.5	31.5		33.4	32.9	+1.9	+1.4
Neck	30.5	31.5		33.4	33.4	+2.9	+1.9
Chest	32.0	31.5		32.4	33.4	+0.4	+1.9
Arm	32.0	32.0		31.9	33.9	-0.1	+1.9
Forearm	32.0	32.0		33.4	33.9	+1.4	+1.9
Finger	31.0	31.0		32.9	32.9	+1.9	+1.9
Abdomen	32.0	32.0		32.4	31.9	+0.4	-0.1
Thigh	31.0	31.5		32.4	32.4	+1.4	+0.9
Calf	31.5	31.5		32.4	31.9	+0.9	+0.4
Ankle	30.5	30.0		32.4	31.9	+1.9	+1.9
Mouth temperature	36.66° C. 98.0° F.			38.0° C. 100.4° F.			
Pulse	92			120			
Time (A.M.)	9:24		9:30	10:45			
Remarks	Basal		In cabinet Inducto- therm	Cabinet opened			

Observations.—Sweating was profuse over the body except in the sympathectomized zone. At the end of experiment there was marked demarcation of flushing on the face. Flushing was absent on the left (sympathectomized) side of face and ear, and was marked on the right ear and right side of the face.

*Differences between first and last readings.

Room temperature, 26.7° C.; temperature of cabinet, 48.33° C.

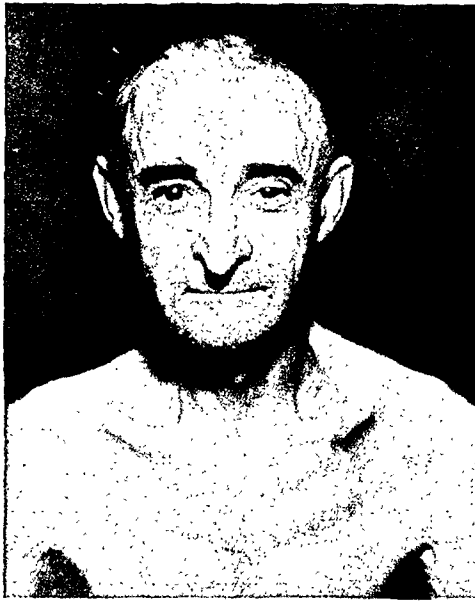


Fig. 1.—Ralph McG., Experiment 3, demonstrating sweating and flushing on the right side of the face only; the left (sympathectomized) side is dry and pale.

This result, as far as flushing is concerned, was always obtained after unilateral cervicodorsal ganglionectomy when the body was heated sufficiently to raise the central temperature, and even though sufficient atropine was administered to prevent sweating.

Experiment 3.—Dec. 5, 1939. Effect of inductotherm.* Ralph McG., 131 days after operation. (Table III.)

Comment.—The temperatures of the middle fingers were equal at the beginning and end of the experiment, and, on the whole, the temperatures did not rise as high as in Experiment 2, although the mouth temperature rose 2.4° F. The demarcation of flushing on the face is given below Table III. (See Fig. 1.)

Experiment 4.—Effect of atropine at room temperature. Ralph McG., 131 days after operation.

Comment.—This was a control experiment, carried out at room temperature (78.0° F.). Atropine (gr. $\frac{1}{45}$) was injected hypodermically, and observations were recorded as in Tables I to III. For a period of an hour there was no rise in skin temperature and no flushing of the face. The mouth temperature fell 0.3° F., and the average fall in skin temperature was 1° C. The blood pressure remained constant, although the pulse rate rose from 96 to 116 beats per minute.

Experiment 5.—Dec. 16, 1939. Effect of inductotherm. Margaret B., aged 31 years, one year after removal of the left inferior cervical and upper three dorsal ganglia (Table IV).

Comment.—The left middle finger was 2.5° C. warmer than the right at the beginning of the experiment. The temperatures were equal at the end of the experiment; that of the right had risen 2.9° C. The mouth temperature rose 2.6° F. There was capillary flushing of only the right side of the face, as noted below Table IV.

TABLE IV
EFFECT OF INDUCTOTHERM ON SKIN

PART	SKIN TEMPERATURE (°C)					
	RIGHT	LEFT		RIGHT	LEFT	
Finger (middle)	30.1	32.6		33.0	33.0	
Mouth temperature	37.2+ C. 99.0° F.			38.7° C. 101.6° F.		
Pulse	84			120		
B. P.	106/70			110/70		
Time (P.M.)	2:15		2:30	4:15		
Remarks	Basal		In cabinet	Cabinet opened		
			Inducto-therm			

Observations.—The head, face, and teeth ached and throbbed at 3:30 P.M. only on the right side (operation had been done for atypical neuralgia on left). There was capillary flushing on the right side of the face; the left remained pale. The demarcation at the midline was definite.

*Differences between first and last readings.

Room temperature, 26.7° C.; temperature of cabinet, 46.7° C.

Experiment 6.—Feb. 3, 1940. Effect of inductotherm and atropine. Mabel R., aged 23 years, 380 days after section of sensory roots C 8 to T 4, inclusive, on both sides, and 331 days after removal of the right inferior cervical and upper two dorsal ganglia (Table V).

Comment.—The right middle finger was 6° warmer than the left at the beginning, and 1° warmer at the end, of the experiment; the temperature of the left rose 8°. The differences in the thumbs and palms were of the same magnitude. The mouth temperature rose 1.8° F. The flushing response is described under Table V.

The oxygen and carbon dioxide content of blood from the median basilic vein was determined with the patient resting at room temperature. (See Table VI.)

*In the Burdick fever therapy cabinet, the inductotherm mechanism is so arranged that it affects the entire body.

TABLE V

EFFECT OF INDUCTOTHERM PLUS ATROPINE ON SKIN

PART	SKIN TEMPERATURE (°C.)						
	RIGHT	LEFT		RIGHT	LEFT	RIGHT*	LEFT*
Forehead	32.9	33.4		32.4	33.9	-0.5	+0.5
Cheek	32.9	32.9		33.4	34.4	+0.5	+1.5
Nose	31.9	31.9		32.9	33.4	+1.0	+1.5
Ears	32.9	32.4		32.4	32.9	-0.5	+0.5
Thumb	33.4	27.4		36.4	35.9	+2.0	+8.5
Finger (middle)	33.4	27.4		36.4	35.4	+2.0	+8.0
Mouth tem- perature	37.0° C. 98.6° F.			38.0° C. 100.4° F.			
Pulse	88			148			
B. P.	114/70			110/62			
Time (P.M.)	2:00		2:05	3:05			
Remarks	Basal Atropine (1/75 gr.) ^H		In cabinet	Cabinet opened			

Observations.—The skin remained dry throughout the test. At the end of the experiment there was a distinct pink flush of the left side of the face, arm, and hand. The right side of the face, arm, and hand were pale. There was a definite line of demarcation on the face.

*Differences between first and last readings.

Room temperature, 27.2° C.; temperature of cabinet, 46.7° C.

TABLE VI

HAND	OXYGEN (VOL. %)	CARBON DIOXIDE (VOL. %)
Right	10.30	49.7
Left	8.15	50.9

These results would indicate a greater minute volume flow of blood in the warmer (denervated) right hand.

TABLE VII

EFFECT OF INDUCTOTHERM PLUS ATROPINE ON SKIN

PART	SKIN TEMPERATURE (°C.)						
	RIGHT	LEFT		RIGHT	LEFT	RIGHT*	LEFT*
Forehead	31.9	32.4		33.6	34.1	+1.7	+1.7
Cheek	31.9	31.9		34.1	34.6	+2.2	+2.7
Nose	30.9	29.9		32.1	32.6	+1.2	+2.7
Ears	30.4	30.4		33.1	33.1	+2.7	+2.7
Thumb	29.4	28.9		35.6	35.6	+6.2	+6.7
Finger (middle)	28.4	27.9		35.6	35.6	+7.2	+7.7
Ankle	31.9	31.4		35.6	36.1	+3.7	+4.7
Toe	32.9	29.4		37.1+	37.1+	+4.2+	+7.7+
Mouth tem- perature	37.2° C. 99.0° F.			39.1° C. 102.4° F.			
Pulse	66			136			
B. P.	204/140			170/130			
Time (P.M.)	3:15		3:20	4:30			
Remarks	Basal Atropine (gr. 1/75) ^H		In cabinet	Cabinet opened			

Observations.—There was no flushing on the face. The left thigh, calf, and foot had a definite pink flush, compared to the pale right thigh, calf, and foot. Sweating occurred only on that part of the back in contact with linen.

*Differences between first and last readings.

†Figures off the instrument scale.

Room temperature, 27.2° C.; temperature of cabinet, 48.3° C.

Experiment 7.—Feb. 5, 1940. Effect of inductotherm and atropine. Eline R., aged 39 years, 449 days after section of anterior and posterior roots T 1 to T 5, inclusive, on both sides, and 504 days after section of the splanchnic nerves and removal of the first and second lumbar ganglia on the right (Table VII).

Comment.—The right large toe was 3.5° warmer than the left at the beginning of the experiment. The temperatures of both rose to 1° off the scale of the instrument but were roughly equal at the end. The mouth temperature rose 3.4° F. There was no flushing on the face, but the left thigh, calf, and foot showed a definite pink flush; the corresponding parts on the right remained pale.

Experiment 8.—Feb. 4, 1940. Effect of inductotherm and atropine. Leah C., aged 33 years, 347 days after section of the anterior and posterior roots T 1 to T 5, inclusive, on both sides, and bilateral chordotomy, and sixteen days after removal of the stellate and first dorsal ganglia on the right (Table VIII).

TABLE VIII
EFFECT OF INDUCTOTHERM PLUS ATROPINE ON SKIN

PART	SKIN TEMPERATURE (°C.)					
	RIGHT	LEFT		RIGHT	LEFT	RIGHT* LEFT*
Forehead	34.6	35.1		35.2	34.7	+0.6 -0.4
Cheek	34.6	34.6		35.2	35.2	+0.6 +0.6
Nose	34.6	34.6		35.2	34.7	+0.6 +0.1
Ears	36.1	36.1		35.7	35.7	-0.4 -0.4
Finger (middle)	34.6	32.6		37.7	37.2	+3.1 +4.6
Mouth temperature	37.2° C. 99.0° F.			38.6° C. 101.4° F.		
Pulse	66			144		
B. P.	178/120			130/90		
Time (P.M.)	3:05		3:25-3:30	4:30		
Remarks	Basal		Atropine (gr. 1/75): In cabinet	Cabinet opened		

Observations.—There was a small amount of moisture on the palm of the left hand only. Otherwise, the skin was dry. The entire face remained pale, without flushing. There was not the slightest evidence of any difference on the two sides. There was a definite difference, however, in the hands and arms on the two sides. The left hand and arm were flushed, whereas the right remained pale.

*Difference between first and last readings.

Room temperature, 26.0° C.; temperature of cabinet, 48.3° C.

Comment.—The chordotomy was bilateral at the level of T 3; a cataract knife was inserted straight into the cord just anterior to the dentate ligament. The sections were 3 mm. deep and 2.5 mm. wide. We do not feel that the chordotomy influenced sweating. In five such cases in which chordotomy was done we were unable to detect any change in thermoregulatory sweating or anything unusual about the skin temperatures after the heat test, unless, in this case, the difference in the temperature of the toes and ankles was caused by the chordotomy.

The right middle finger was 2° warmer than the left at the beginning, and 0.5° warmer at the end of the experiment; the temperature of the left rose 4.6°. The mouth temperature rose 2.4° F. The interesting flushing response is described in Table VIII.

DISCUSSION

As was reported in a recent paper,¹ we have found that section of the anterior roots T 1 to T 5, inclusive, on both sides, practically abolishes

thermoregulatory sweating on the face. It may be diminished down to the level of T 2 or T 3, but sweating is usually abundant on the neck and normal on the upper extremities. After removal of the inferior cervical and upper two dorsal ganglia, sweating is abolished on the ipsilateral side of the face, neck, and upper extremity, and the line of demarcation is sharp. We believe that the distribution of fibers to arterioles and capillaries closely agrees with the distribution to sweat glands.

Substantial changes in skin temperature after ganglionectomy occur only on the hands, fingers, ankles, and toes and are most marked on the tips of the fingers and toes. Although it is sometimes stated that the ipsilateral side of the face is warmer in Horner's syndrome, we have never been able to verify this and find that the ears, nose, and cheeks do not become relatively warmer after cervicodorsal ganglionectomy before or after time for postganglionic degeneration has elapsed, even though the relative warmth of the hand and fingers may be marked.

The relative increase in the temperature of the hand and fingers after cervicodorsal ganglionectomy may vary from no change to a difference of 5° or 6° C., and this is true either before or after degeneration has occurred. If the hand is warmer after ganglionectomy, it remains warmer than its mate (in the nonvasospastic subject). At least this has been true in our cases for as long as 1.5 years after operation. We have not encountered a single case in which the sympathectomized hand became colder in the absence of vasospastic disease. There was no significant relative change after operation in Ralph McG. (Experiment 1). We have found that this is usually true in patients of his age (55 years), or older. After lumbar ganglionectomy, however, there has always been a relative rise in temperature of the toes, in our experience. The change in temperature of the skin after sympathectomy is an indication not only of the flexibility of the arterioles, but of the degree of vasospasm imposed through the sympathetics. It appears that this control is diminished with age, and this may be more true of the upper than of the lower extremities.

In the cases reported here, the maximum relative difference in the temperature of the fingers after unilateral cervicodorsal ganglionectomy was 6° C. (Mabel R., Experiment 6). The difference in the toes of Eline R. (Experiment 7) after lumbar ganglionectomy was 7° C.

The skin temperature never became equal to the mouth temperature with any method of heating. Excepting the hands and feet, the skin temperature rises about as much as the mouth temperature.

No matter what the difference was in the temperature of the fingers or toes on the two sides at the beginning, the two sides were equal at the end of a heating experiment. Lewis and Pickering¹³ stated that denervated skin rarely becomes as warm as the normal side when heated,

and they attribute the failure of maximal dilatation to interruption of vasodilator fibers. Our results do not agree with this, and for a definite reason. Their subjects were placed in a heating cabinet with the hands outside. Hence they were measuring only the central thermoregulatory effect on the hands. The sympathectomized hand would not be expected to warm under these conditions, at any rate not more than the rise in blood temperature. The hands of our subjects were in the heating cabinet, and hence we were measuring the first order, or peripheral action, of heat on the vessel itself. Kunkel, Stead, and Weiss¹⁸ found that local heat of 43° C. produces nearly complete vasodilatation in the skin.

There are three different methods of studying a sympathectomized hand and its reaction to a change in temperature: (1) The body may be subjected to a change in temperature in a cabinet with the hands outside;¹³ (2) the body may be placed in a constant temperature cabinet with the hands outside and the outside temperature changed (Ascroft¹⁹); and (3) the entire body may be placed in a cabinet the temperature of which is changed (Hyndman and Wolkin,²⁰ experiments herein reported). In the first method one studies the third order reaction alone. Lewis and Pickering¹³ found that, under these circumstances, when the environmental temperature of the body was changed, the skin temperature of the normal hand changed accordingly, that is, it increased when the body was heated. The sympathectomized hand, however, underwent no change because its central sympathetic connections had been interrupted.

In the second method one studies, in our opinion, essentially the first and second order reactions.

In the third method one studies a combination of first, second, and third order reactions. We found, as demonstrated in this report, that, when the entire body is heated with the hands inside the cabinet, the skin temperatures of the sympathectomized and normal fingers finally always become equal, no matter what the difference may be at room temperature. In an investigation of the effect of severe cold, the results of which are to be published,²⁰ we found that, when the nude subject was placed in a refrigerator at a temperature of 0° to 6° C., the temperature of the fingers on both sides declined markedly, but not quite as much on the sympathectomized as on the normal side.

The fact that the temperatures of the fingers on the two sides were always equal at the end of our heating tests would indicate that arteriolar vasodilatation becomes maximal. After sympathectomy has produced some dilatation of arterioles, the latter can be dilated still further by applying heat.

If we let A represent the vasodilation, or, rather, the increase in skin temperature that results from only the local effect of heat on the vessel itself (first order reaction), then the fact may be expressed as follows:

The relative increase in the temperature of a finger after sympathectomy plus A equals the increase in the temperature of the normal finger that results from centrally controlled (second and third order) vasodilation,* plus A. This is true if the parts measured are subjected to the same external heat, and if this heat is sufficient to bring about maximal vasodilation.

EVIDENCE FOR THE EXISTENCE OF CENTRALLY CONTROLLED CAPILLARY DILATOR FIBERS

We refer to *capillary* dilator fibers because our conclusions depend upon a visible change due to capillary dilatation. Capillary dilatation may be only a part of a general vasomotor dilator mechanism. The evidence for the existence of an active vasodilator mechanism in general is summarized by Starling.²¹ Stimulation of the cut end of the chorda tympani causes dilatation of the vessels in the submaxillary gland. Other dilator nerves are the small petrosal nerve to the parotid gland, the lingual nerve to the blood vessels of the tongue, and the pelvic visceral nerves to those of the penis. There are two anatomic differences between these examples and the skin dilators which we have observed. The cell bodies of the fibers in the former lie close to the structures which they innervate, as is generally the case with parasympathetics, whereas no comparable cell bodies have been demonstrated in the skin. Secondly, fibers in the former case leave in company with craniosacral nerves, whereas those to the skin vessels are strictly thoracolumbar. In the dog, dilatation of the vessels of the soft palate and gums can be produced by stimulation of the cervical sympathetic of the same side, and these fibers may be homologous with those of the skin. Starling points out that vasodilator nerves can be demonstrated in mixed peripheral nerves, i.e., sciatic, by stimulating the peripheral cut end with repeated induction shocks at slow intervals, or by taking advantage of the apparent fact that the degeneration times of vasoconstrictors and vasodilators are unequal.

Stimulation of the peripheral end of a sensory root causes dilatation of skin vessels in the distribution of the sensory nerve.²² It is probably because of this fact that there has been a tendency to believe that the sympathetic vasodilators of the skin course with the posterior roots. We believe that this antidromic response, as demonstrated by Bayliss, operates in the same manner as does the axon reflex after the intra-

*We do not wish to commit ourselves on what proportion of this central arteriolar vasodilation is active and what proportion is accounted for by inhibition of vasoconstriction. The conclusion which we should be forced to draw at present is that, since the temperatures are always equal on the two sides at the end of a heating experiment, there is no evidence of the existence of arteriolar vasodilator nerves. We cannot quite correlate this conclusion with the results of Lewis and Pickering.¹³ If the patient's hands are outside the heating cabinet, and hence constantly at room temperature, we might say that the sympathectomized hand exhibits a first order vasoconstriction incident to room temperature and that this first order response in the normal hand is overcome by central reflexes. Is this inhibition of vasoconstriction or active vasodilation? It seems to us that, if it is considered to be the former, one would have to concede that it is central inhibition of a first order vasoconstriction.

cutaneous injection of histamine.* The phenomenon does not necessarily indicate that the sympathetic vasodilator nerves course in the posterior roots. The evidence that we have indicates that capillary dilator fibers course in the anterior roots.

Crawford²³ pointed out that the evidence for the existence of vasodilator nerves to the capillaries of the skin is much less certain than that for vasoconstrictor nerves to the capillaries. He quoted the investigators who believe that capillary vasodilators exist, and gave a good bibliography relevant to the subject of capillary innervation. Crawford himself produced evidence to prove the existence of skin capillary vasoconstrictors. He observed the effects on the ear of the albino rabbit of artificially stimulating the cervical sympathetic nerves. The result was always contraction of the capillary.†

Lewis and Landis²⁴ observed flushing limited to the normally innervated side, after unilateral cervicodorsal ganglionectomy, when the patient was heated. They also observed that emotional blushing was limited to the normally innervated side in such cases. They concluded that emotional blushing required intact sympathetic nerves. They expressed doubt that heat flushing was caused only by an inhibition of vasoconstrictor tone.

The evidence for the existence of active vasodilators to the skin and for the fact that they course in the anterior roots of the thoracolumbar division is drawn from the following observations.

1. We observed that after unilateral cervicodorsal ganglionectomy patients in the heat cabinet occasionally would exhibit a definite capillary flushing on the normal side of the face while the denervated side remained pale. The line of demarcation in the mid-sagittal plane was definite. We found that, if they were heated sufficiently or placed in the inductotherm with or without receiving atropine, the unilateral flushing would always appear. It might be argued that this phenomenon is caused by inhibition of vasoconstriction rather than active dilatation. If this were true, however, one would expect it (flushing on the operated side) to occur after ganglionectomy. We have never observed any semblance of it, although we have watched for it. We have seen it in a mild form on the hands immediately after ganglionectomy. Brown and Adson²⁵ observed no color changes or demonstrable variations in the capillaries after lumbar ganglionectomy on nonvasospastic patients.

*We have studied the histamine reaction in many patients after preganglionic sympathectomy, after postganglionic sympathectomy before and after degeneration was complete, after extensive anterior rhizotomy and posterior rhizotomy, and the two combined, early and late following operation, after complete transverse lesions of the cord, and after spinal anesthetics. We found normal flares and wheals in all of these cases. The only lesion we did not have was a complete degeneration of a somatic sensory nerve. It is known that the histamine reaction is absent after complete degeneration of a peripheral nerve, and hence the deduction that the phenomenon is an axon reflex of a somatic sensory nerve. We have not reported this study because it confirms only the known facts.

†Since there is such strong evidence for the existence of two types of fibers in the thoracolumbar sympathetic system, one is handicapped in drawing rigorous conclusions from the results of artificially stimulating sympathetic nerves. We have shown that the integrated response to severe heating (this paper) and to severe cooling²⁰ is capillary dilatation. Transient blanching precedes dilatation in the latter case.

They stated: "There has not been evidence in any case of this series, at least with the methods available, to indicate that capillary dilatation follows interruption of the vasomotor nerves." On one occasion the flushing was present on the normal side during ether anesthesia in one of our patients with a Horner's syndrome caused by Hodgkin's disease. The pathologic side remained pale.

2. After the injection of pilocarpine (gr. $\frac{1}{5}$), we observed this flushing on the denervated side in one case. It was mild, but definite. We do not have evidence that arterioles become sensitized to pilocarpine after ganglionectomy, and this phenomenon occurred in only one case. We do believe that in this instance the pilocarpine acted peripherally, that the capillaries were more sensitive on the denervated side, and that this caused the unilateral flushing.

3. It may be argued that the flushing is due to release of acetylcholine in the tissues as a result of heating. The inhibition of sweat end plates by atropine would help to rule out the possibility that these were a source of acetylcholine, and, in addition, atropine should be able to neutralize any acetylcholine that might be liberated.

It is recognized that, although small amounts of acetylcholine cause capillary dilatation, larger amounts may cause constriction. Hence it may be supposed that, after postganglionic fibers have degenerated, the capillaries become sensitized, so that an amount of acetylcholine which will cause dilatation on the normal side will cause constriction on the denervated side. We feel that the results in the case of Leah C. (Experiment 8) refute this criticism and establish the phenomenon as one of centrally controlled capillary dilatation. In this case the anterior and posterior spinal roots from T 1 to T 5, inclusive, on both sides were severed. In addition to this, a cervicodorsal ganglionectomy was done later on the right. The sweat test demonstrated absence of sweating on the entire face and on the right upper extremity. Therefore, she had a preganglionic sympathectomy affecting the left side of the face, and a postganglionic sympathectomy affecting the right side of the face and right upper extremity. The inductotherm, plus atropine, caused no flushing whatever on the face, but the left hand was flushed and the right was pale.

If this evidence for the existence of capillary vasodilators be accepted, do they course through the anterior roots, as do other efferent sympathetics, or do they reside in the posterior roots? We believe that the following evidence indicates that they are contained in the anterior and not in the posterior roots.

Mabel R. (Experiment 6) had had the posterior roots, only, severed from C 8 to T 4, inclusive, on both sides. Later a cervicodorsal ganglionectomy was done on the right. The heating test brought out good flushing on the left side of the face and none on the right.

One patient who had the posterior roots severed from T 1 to T 10, inclusive, on both sides, showed marked flushing of the face, chest, and arms in the inductotherm while under the influence of atropine (flushing is not as evident below the chest unless the two sides differ for comparison).

It is of interest that one patient, after triple ligation of the left common carotid artery with silk, exhibited marked flushing on the face during the heat test (dry heat only), and that there was no difference on the two sides.

EFFECT OF HEATING ON PULSE RATE AND BLOOD PRESSURE

The pulse rate at the end of the heating experiment was markedly increased, often to twice its previous rate. The blood pressure was usually somewhat decreased, and especially so in cases of essential hypertension (Experiments 7 and 8).

CONCLUSIONS

1. The fingers and toes exhibit the greatest rise in temperature when the body is heated.

2. After unilateral sympathectomy the skin temperature of the fingers or toes will be about equal on the two sides at the end of a heating experiment of the type herein described, regardless of their previous difference, provided these parts were contained in the heating cabinet.

3. Therefore, a sympathectomized arteriole of the skin is capable of dilating as a result of the effect of heat on the vessel itself.

4. Capillary dilator fibers, which are probably a part of a general vasodilator mechanism, supply the vessels of the skin and are centrally controlled. These fibers course through the anterior roots of the thoracolumbar nerves, and thence through the sympathetic ganglia.

5. Since sympathectomy results in a significant rise in skin temperature in only the carpal and pedal extremities, it is logical to deduce that, at room temperatures, the sympathetics do not have much of a constricting effect on the skin vessels except those of the hands and feet.

6. Body temperature under ordinary and average conditions, so far as the skin is concerned, is no doubt maintained largely by responses of the vessels themselves to external stimuli. The central mechanism functions (a) as a governor over the peripheral mechanism, and hence manifests itself more strongly when the need is extreme, and (b) as a mechanism for utilizing or integrating the entire skin surface for heat conservation or dissipation when only a part is subjected to a changing temperature. (These facts will be made more evident in subsequent reports.)

REFERENCES

1. Hyndman, Olan R., and Wolkin, Julius: Sweat Mechanism in Man. Study of Distribution of Sweat Fibers From the Sympathetic Ganglia, Spinal Roots, Spinal Cord, and Common Carotid Artery, *Arch. Neurol. & Psychiat.* 45: 446, 1941.

2. Head, H., and Riddoch, G.: The Automatic Bladder, Excessive Sweating and Some Other Reflex Conditions, in *Gross Injuries of the Spinal Cord*, Brain 40: 188, 1917.
3. List, Carl F., and Peet, Max M.: Sweat Secretion in Man. I. Sweating Responses in Normal Persons, *Arch. Neurol. & Psychiat.* 39: 1228, 1938.
4. Sahs, A. L., and Fulton, J. F.: Somatic and Autonomic Reflexes in Spinal Monkeys, *J. Neurophysiol.* 3: 258, 1940.
5. Gibbon, John H., and Landis, Eugene M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, *J. Clin. Investigation* 11: 1019, 1932.
6. Fulton, J. F.: *Physiology of the Nervous System*, New York, 1938, Oxford University Press, p. 247.
7. Higier, Heinrich: *Vegetative Neurology, Nerve. & Ment. Dis. Monograph Series No. 27*, Translation by Kraus, W. M., New York, 1919, Nerv. & Ment. Dis. Publishing Co., p. 33.
8. List, C. L., and Peet, M. M.: Sweat Secretion in Man. III. Clinical Observations on Sweating Produced by Pilocarpine and Mecholyl, *Arch. Neurol. & Psychiat.* 40: 269, 1938.
9. Guttman, L., and List, C. F.: Zur Topik und Pathophysiologie der Schweisssekretion, *Ztschr. f. d. ges. Neurol. u. Psychiat.* 116: 504, 1928.
10. Guttman, L.: Die Schweisssekretion des Menschen in ihren Beziehungen zum Nervensystem, *Ztschr. f. d. ges. Neurol. u. Psychiat.* 135: 1, 1931.
11. Dale, H. H.: Progress in Autopharmacology: II. Acetylcholine; Its Natural Occurrence and Probable Function, *Bull. Johns Hopkins Hosp.* 53: 312, 1933.
12. Dale, H. H., and Feldberg, W.: The Chemical Transmission of Secretory Impulses to the Sweat Glands of the Cat, *J. Physiol.* 82: 121, 1934.
13. Lewis, Thomas, and Pickering, Geo. W.: Vasodilatation in the Limbs in Response to Warming the Body; With Evidence for Sympathetic Vasodilator Nerves in Man, *Heart* 16: 33, 1931.
14. Ranson, S. W., and Ingram, W. R.: Hypothalamus and Regulation of Body Temperature, *Proc. Soc. Exper. Biol. & Med.* 32: 1439, 1935.
15. Talbot, Fritz B.: Skin Temperatures of Children, *Am. J. Dis. Child.* 42: 966, 1931.
16. Benedict, F. G., and Parmenter, H. S.: Human Skin Temperature as Affected by Muscular Activity, Exposure to Cold, and Wind Movement, *Am. J. Physiol.* 87: 633, 1928.
17. Bumke, O., and Foerster, O.: *Handbuch der Neurologie*, Berlin, 1936, Julius Springer, Vol. 5, p. 37.
18. Kunkel, Paul, Stead, Eugene A., and Weiss, Soma: Blood Flow and Vasomotor Reactions in the Hand, Forearm, Foot, and Calf in Response to Physical and Chemical Stimuli, *J. Clin. Investigation* 2: 225, 1939.
19. Ascroft, P. B.: The Basis of Treatment of Vasospastic States of the Extremities: An Experimental Analysis in Monkeys, *Brit. J. Surg.* 24: 787-816, 1937.
20. Hyndman, Olan R., and Wolkin, Julius: The Autonomic Mechanism of Heat Conservation and Dissipation. II. Effects of Cooling the Body. A Comparison of Peripheral, and Central Vasomotor Responses to Cold. *AM. HEART J.* (In press).
21. Starling, Ernest H.: *Principles of Human Physiology*, ed. 7, Philadelphia, 1936, Lea & Febiger, p. 800.
22. Bayliss, W. M.: On the Origin From the Spinal Cord of the Vasodilator Fibers of the Hind-Limb, and on the Nature of These Fibers, *J. Physiol.* 26: 173, 1901.
23. Crawford, J. Hamilton: The Influence of the Sympathetic Nervous System on the Capillaries During Peripheral Stasis. The Vegetative Nervous System. An Investigation of the Most Recent Advances, *Proc. of Assoc. for Research in Nerv. & Ment. Dis.*, Vol. 9, Baltimore, 1930, The Williams & Wilkins Co.
24. Lewis, T., and Landis, E. M.: Some Physiologic Effects of Sympathetic Ganglionectomy in the Human Being and Its Effect in a Case of Raynaud's Disease, *Heart* 15: 151, 1929.
25. Brown, George E., and Adson, Alfred W.: Physiologic Effects of Thoracic and Lumbar Sympathetic Ganglionectomy or Trunk-Section, *Proc. of the Assoc. for Research in Nerv. & Ment. Dis.* Vol. 9, p. 721-765, Baltimore, 1930, The Williams & Wilkins Co.

SPINAL CORD ISCHEMIA IN DISSECTING AORTIC ANEURYSM

E. L. TUOHY, M.D., P. G. BOMAN, M.D., AND GEORGE L. BERDEZ, M.D.
DULUTH, MINN.

SUDDEN, severe, sustained chest pain, with or without radiation, is often caused by coronary disease. So well did Herrick^{1, 2} impress this fact upon the profession that surgeons, as well as internists, at times overdiagnose coronary occlusion, and fail to consider other important conditions with an overriding symptomatology. Hamman^{3, 4} ably discussed these entities, including pericarditis, mediastinal emphysema, pulmonary embolism, and esophageal hiatus herniation, and he conspicuously mentioned aortic aneurysmal dissection. Most of his discussion concerned the chest.

The subject of dissecting aneurysm of the aorta is well covered in the literature. Crowell⁵ wrote a comprehensive review. From his culling of forty references one learns that the disease has been recognized for nearly a century and a half. Crowell's material consisted chiefly of LeCount's autopsy cases. A consideration of the anatomic observations, therefore, predominates. The article does not lack clinical influence, however, as this excerpt amply testifies: "Very little attention has been paid to the interference with the circulation in the branches of the aorta caused by the splitting of the walls at the places where such branches have their mouths; and it may be safely assumed that the failure to recognize dissecting aneurysms of the aorta during life is at least in part due to failure to appreciate the fact that symptoms of this condition may be produced by interference with the blood supply in these branches. Only a few of the reports examined refer to the amount of the circumference of the aorta dissected at different distances in its length, or to the location of such circumferential splitting." It is evident that this is still true and that more correct ante-mortem diagnoses would have been made if clinicians had been aware of this diagnostic fact.

Holland and Bayley⁶ have reported nineteen additional cases of dissecting aneurysm. They reviewed with especial care the theories concerning the cause of the initial intimal tears and the ultimate circular and linear extensions. Their cases illustrate, as do ours, the decided tendency toward rupture into the pericardial cavity (eight cases), and into either the left pleural cavity (four cases) or the mediastinal tissues (four cases). In one instance there were dissection and hemorrhage into both the left pleural cavity and the mediastinum. However, only in connection with Case 12 did the authors make any comment concerning neurological changes in the legs. The 38-year-old woman

From the Department of Internal Medicine, the Duluth Clinic, and the Department of Pathology, St. Mary's Hospital, Duluth.
Received for publication Sept. 30, 1940.

"four days previously," they stated, "had been seized with a sudden excruciating pain in the chest which gradually extended to the toes. Later there was impairment of motion in the lower extremities, which became numb and cold." They mentioned further that thrombi were found in the pulmonic, splenic, and superior mesenteric arteries; and evidently enough heat was applied to the extremities to cause some damage to the skin. This might imply that the attendant suspected occlusion of the vessels supplying the legs; this was not found at autopsy.

Shennan⁷ was able to find in the literature only six bona fide cases in which the correct diagnosis was made during life. When Rogers⁸ made his report, he was able to collect four additional cases in which the diagnosis had been made and added three of his own. Rogers' article gave us our first appreciation of the relationship between aortic wall dissection and sensory changes or motor paralyses of the legs incidental to sudden interruption of an important portion of the collateral blood supply to the cord. This follows a pinching off or obliteration of segmental (intercostal and lumbar) arteries which arise from the descending and abdominal aorta. These important vessels bilaterally augment the vertebral arterial blood supply (coming down from above) through the pia mater of the cord.*

We have chanced upon a series of these dissections, in which there were lower extremity symptoms, within a comparatively short period. We have asked ourselves, "Why is it that these signs have not been encountered before in cases of aortic wall dissection?" We have put this question to men who have had much experience with cardiovascular disease. It seems to have been the rule to pay little attention to the lower portion of the body, perhaps because attention was focused upon an acutely ill patient afflicted with gripping and tearing pain who died shortly after he was first seen. Nevertheless, not all of these patients die immediately. Rogers reported one man who lived twenty-seven months. A woman whose aneurysm was correctly diagnosed by one of us (E. L. T.) during life lived just short of three months. Hirschboeck and Boman⁹ reported the case of a man who survived for nearly four months after a crushing attack and an extensive dissection within the thorax; rupture into the left pleural cavity ultimately occurred. In Case 5 of Hamman's series, the patient lived approximately sixteen months. Under many circumstances there must be sufficient time and opportunity not only to study the lower portions of the body carefully, but in instances of earlier demise to tell the pathologist what is suspected. He may then go farther than "determine the cause of death," and make a more careful examination of the aortic arterial branches which are interrupted at their ostia, as well as examine and appraise the degrees of damage or integrity of the cells of the spinal cord.

*Since the article by Rogers adequately outlines and explains this situation, and since his deductions and experiences so fully coincide with our own, we feel that it is unnecessary to indulge in repetition.

We regret that there was no autopsy in one of our cases. We are reporting in detail one illustrative case. The other reports are abridged. The comparative features are commented upon.

CASE 1.—A married man, aged 54, was employed as an engineer. Four days previous to entering St. Mary's Hospital, he complained of a moderately severe pain in his lower back. This gradually progressed upward and into his chest. He likened it to a pleuritic pain because it was increased on inspiration. At noon, on Feb. 5, 1940, after hanging a fairly heavy door, he had a feeling in the abdomen as if he should go to stool. He did so, but, in attempting to get up, found he could not use his legs. Fellow workmen assisted him into the ambulance and to the hospital. On the examining table in the emergency room he asked the intern in attendance, "Are my legs on the table or off?" No reflexes could be elicited, and sensation in his legs was gone. While he was being examined he had a severe, sudden pain in the abdomen, and it was noted that he became both dyspneic and cyanotic. However, he asked for and took a few puffs from a cigarette and felt somewhat better. After he had been taken to his room, he became fully conscious and with the abatement of his abdominal pain stated that, although he was aware of his legs, he felt as if they were detached from his body. Two hours later he complained of violent pain in the upper abdomen and in his chest. "He drew up his legs on his abdomen as if in extreme pain," says the intern's notes, "became dyspneic, pulseless, and died."

At necropsy* the heart weighed 610 Gm. There was abundant evidence of extensive arterial decay, associated with hypertensive disease. There was a separation of the coats of the aorta all the way from the aortic bifurcation to the base of the aorta. There was a slitlike tear in the pericardium, producing an ultimate communication from the inside of the aorta, in its first portion, with the pericardial sac. The pericardium contained 250 c.c. of partially clotted blood. The inner aortic layers could be easily peeled off from the outer, and, especially in the abdominal aorta, there was extensive degeneration, with small intimal defects and some calcium deposit.

This interesting item from the autopsy protocol is quoted because of the bearing it has upon whether the symptoms of paralysis in these cases are the result of ischemia of the spinal cord, or of direct ischemia of the limbs, such as that produced, for example, by a saddle embolus. "The aneurysmal dissection extends downward posteriorly and laterally. At a point just above the aortic bifurcation the intimal layer of the aorta is rolled up near a site of rupture, causing almost complete obstruction of the hypogastric arteries. The intima of the hypogastric arteries is likewise displaced, almost completely obstructing their lumina."

COMMENT

The question of the role played by vascular occlusion in the extremities, relative to that of anoxia of the cord, is not likely to confuse anyone who has observed what happens when embolism, either of the main arteries of the leg or of the saddle type, causes obstruction at the bifurcation. Despite the fact that a definite impediment to blood flow may exist, as in this case, the succession of events and symptoms is decisively

*The autopsies in our cases were done by Dr. George L. Berdez, pathologist at St. Mary's Hospital, Duluth.

†This is a very characteristic site of rupture, and means that there is a particular weakness in the aortic wall at that point, or that it is subject to peculiar hydrostatic trauma because of its position. In this case, as in others, there was considerable leakage under the epicardium and the serosa of the aorta. The indirect opening into the pericardial sac, producing hemopericardium, is not infrequently located at some distance from the rupture of the aorta itself.

and dynamically different. This man did not live long enough to show much change or "vacillation" in either his motor or sensory manifestations. Nevertheless, he was totally unable to move his legs when he was brought to the hospital and had lost all sensation in his legs. Then, just prior to death, he was able not only to comment about perverted sensation in his legs, but to draw them forcibly up against the abdomen. Unfortunately, the cord was not examined at autopsy. Had it been, it is not likely that any gross change would have been found because of the relatively short period of ischemia. With respect to the collateral circulation to the cord directly from the aorta, we must not forget that it may change from hour to hour; it depends not only upon mechanical obstruction, but degree of arterial spasm, as well. This physiologic propensity to spasm which accompanies trauma and pain in various portions of the body is now well understood. In this instance the dissection began within the abdomen, and this emphasizes the impression given by various authors that the initial break may not be within the intima itself, but rather a leak from the vasa vasorum of degenerated tissues and vessels, where the dissection up and down separates the aortic layers before either internal or external rupture.

CASE 2.—Within six weeks of the above experience, one of us (P. G. B.) was called in consultation by Dr. J. W. Ekblad to see a delivery man, aged 40 years. He appeared previously to have been in good health. After a heavy, wet snow in March, 1940, he attempted to put chains on the rear wheels of his truck. This was a difficult task, and rather strenuous pulling and jerking were necessary. He was suddenly seized with a choking sensation and a pain in his throat, with radiation down his back of a "hot, searing character." He rested for a few minutes, then walked about a block and climbed one flight of stairs to the doctor's office, where he collapsed. He was given a hypodermic injection of morphine and brought immediately to St. Mary's Hospital. When he was examined about two hours later, he had lost the sensation in both lower extremities and was unable to use his legs. Associated with this was a loss of sensation, or numbness, which began at a very definite level just above the umbilicus and involved all of the body below that point. On the following day (twenty-four hours after the onset), the patient stated that sensation was gradually returning in the abdomen and thighs and to a lesser degree in the left leg. The paralysis on the left side had almost completely disappeared and on the right side had very materially decreased. The blood pressure was normal. The reflexes were absent on the right side, but there was no change on the left.

The clinical impression was that he had had a hemorrhage into the spinal cord, because of the very definite level at which the sensory response was lost and because of the bilateral paralysis below that level. No detailed neurological examination was made. The man was in fair comfort for the next twenty-four hours, when he suddenly died. Before the autopsy one of us (E. L. T.) made the statement that, in view of our previous experience, nothing but dissecting aneurysm could account for his symptoms and signs; and thus, we may say that (belatedly) a correct diagnosis was made before the autopsy, if not before death.

The autopsy findings were almost the same as in Case 1. In this instance the heart weighed 400 Gm.; the evidence of arterial degeneration was not nearly so marked. The dissection had extended just above the aortic valves and down to the bifurcation of the right iliac artery. The dissection was more marked on the right

than on the left side; this was in keeping with the symptoms. A cross section of the right common iliac artery showed that the intimal layer was separated sufficiently to close the vessel almost completely. The mouths of the intercostal and lumbar arteries on the right side of the aorta were torn partially or separated. The aneurysm had ruptured into the pericardial sac, which contained 700 c.c. of blood.

COMMENT

This man, who was sixteen years younger than our first patient and showed much less evidence of hypertensive disease, nevertheless had arterial weakness which, under great strain, was sufficient to cause rupture and death. From the standpoint of treatment, of course, the correct diagnosis could not have been of any especial advantage to the victim.

CASE 3.—A divorced man, aged 73 years, was brought to St. Mary's Hospital on Feb. 13, 1940. At 8 A.M. of that day he had had a terrific pain in the lower back and, when he attempted to get up, could not stand on his legs. He entered the hospital at 2 P.M., complaining of a sense of pressure all over the lower abdomen, and pain in his back. At 9 P.M. he had an attack which lasted about an hour, with moderate dyspnea and some cyanosis. Morphine gave relief. During the next two days, and while he was quiet in bed, there was persistent numbness in his legs; he was unable to void and had to be catheterized. On Feb. 17, 1940, the left leg was still numb and was moved with difficulty; the right leg could be drawn up, but it did not feel natural.

One of us (E. L. T.) was called in consultation on Feb. 18, 1940, by Dr. C. E. Vercellini, who had been attending the man for several years. In the previous history there was nothing eventful. Although his blood pressure had varied from time to time, it held an average level of about 160/100. Several blood Wassermann reactions had been negative. The patient seemed to be comfortable but had a dusky color. There was a good pulse in the dorsalis pedis on both sides. Although he could draw his legs up, he stated that they felt very heavy, and he had little desire to attempt to use them in standing. He spoke of little pain, but mentioned feeling "as though there were a covering over the skin." There were no cardiac abnormalities. Since we had presented the post-mortem observations in our Case 1 at our weekly clinicopathologic conference, Dr. Vercellini had made a provisional diagnosis of dissecting aortic aneurysm. The future course was fully in keeping with that diagnosis.

On the morning of February 21 (eight days after entering the hospital), he appeared tired and depressed and complained of a sense of oppression within the chest. At noon the intern was called because the patient had suddenly become cyanotic and pulseless. He died within a few minutes.

COMMENT

We were denied an autopsy, and the diagnostic impression of aortic aneurysmal dissection rests chiefly upon the sudden abdominal pain, with loss of motion and feeling in the legs, upon the gradual improvement and beginning rehabilitation that followed, and upon the sudden demise that may well have been caused by cardiac tamponage.

CASE 4.—One of us (G. L. B.) performed an autopsy upon a man, aged 78 years. Fig. 1 shows a line of automobiles, with one on the wrong side of the road. The blot of oil indicates the force of the collision. The driver of the car on the proper

side of the road foresightedly took this picture, as well as that shown in Fig. 2. The driver of this erratic car is obviously dead. The tight skin and the prominent veins of the hand clearly indicate his age.

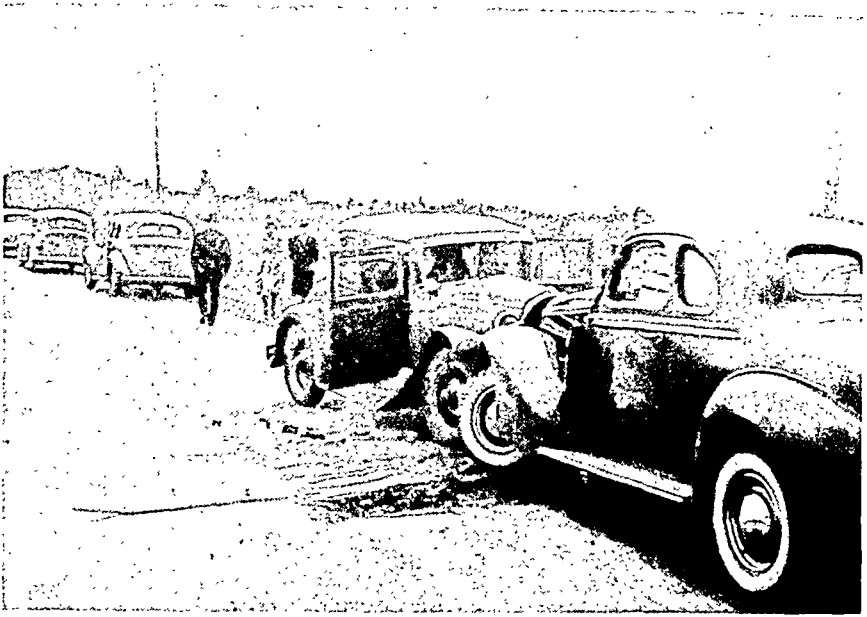


Fig. 1.—The car containing the victim shown on the wrong side of the road.



Fig. 2.—The driver of the erratic car.

This was a case of immediate, sudden death. The autopsy showed "fractures of all the ribs from the first to the seventh on the left side, and of the costal cartilages of the second, third, seventh, and eighth ribs on the same side. *There was no hemorrhage* whatever at the site of the fracture. There was also a fracture of the tibia on both sides, likewise without hemorrhage." He died of "rupture of the upper thoracic aorta and beginning dissecting aneurysm. There was extensive hemorrhage into the posterior mediastinum and an accumulation of 200 c.c. of blood in the left pleural cavity."

COMMENT

Without a necropsy, or the collateral evidence of the car wandering across to the opposite traffic lane, this death would have been attributed to the crushing chest injury, although, as a matter of fact, the man was dead from aortic rupture and mediastinal hemorrhage before the cars collided.

CASE 5.—One of us (E. L. T.) correctly diagnosed, before death, a previously unreported instance of aortic wall dissection in a woman, aged 67 years. She died May 29, 1933. She had been treated for several years for hypertensive disease. Two and one-half months prior to death she entered St. Mary's Hospital with an acute, sudden, crushing pain in the chest which was attributed at the time of onset to coronary thrombosis. However, she developed two signs which were incompatible with uncomplicated coronary thrombosis. After a few days a diastolic murmur appeared at the aortic area. This most certainly had not been there before. It was noticed also that a pulsating tumor developed in the upper abdomen, just above the navel. A careful review of the old chart fails to reveal any comment about leg symptoms, except the statement that on entering the hospital she was unable to walk.

The autopsy disclosed the same sort of extensive dissection as in Cases 1 and 2. She had the customary break through the first portion of the aorta within the pericardial reflection. There were 350 c.c. of unclotted blood in the pericardial cavity. The dissection extended downward into the iliacs. Old clots in the outer channel formed the bulge where the upper abdominal tumor had been palpated. *The aortic valves and ring were intact.*

COMMENT

When chest and upper abdominal symptoms predominate, a suddenly appearing diastolic murmur is as diagnostic of supraortic ring dissection as "wandering" paralysis and anesthesia in the legs are of lower aortic wall dissection. Galbraith and Hardwick¹⁰ discussed this feature fully in an excellent case report. They mentioned the reports and opinions of Hamman and Apperly, as well as those of Resnik and Keefer,¹¹ and favored the latter's explanation and that attributed to Letulle¹²; namely, that "the signs can be accounted for by the ebb and flow from the aorta into the aneurysmal pouch." This implies, and is in keeping with our inference, that the ultimate pericardial sac flooding is a terminal event.

The question remains whether thoracic aortic wall dissection could interfere with either brain or cervical cord circulation sufficiently to cause interruption of nerve impulses to the face or the upper extremities. On theoretical grounds it would appear unlikely that such interruptions could easily produce symptoms comparable to those which occur in the legs. With the exception of certain embolic phenomena, vascular accidents in the upper area rarely are seen. However, our most recent experience is presented for what it may be worth.

CASE 6.—A widow, aged 82 years, died suddenly on April 22, 1940. One of us (P. G. B.) had attended her at his office and at her home over a period of twelve years. Her blood pressure had ranged well above 200/120 for about five years. She

showed unmistakable evidence of cerebral arteriosclerosis. She developed food idiosyncrasies and complained of obstipation. On the morning of the day she died she complained, after straining at stool, of some fleeting dizziness. This passed off, but she remained quite weak and drowsy and slept several hours during the day. In the late afternoon the daughter noticed that she had difficulty with her speech, and there appeared to be a weakness or paralysis of the right side of the face. This lasted for only about an hour, at which time the patient felt better and seemed to be recovering. The family left her for a short time during dinner, and, when they returned, she was dead.

Autopsy revealed advanced arteriosclerotic changes within the aorta, and there was a moderate-sized aneurysm of the left common iliac artery. An aneurysmal dissection was beginning just above the aortic ring, with the same type of opening into the pericardial sac as in the other cases. The pericardium contained 840 c.c. of blood, and there was a bilateral hydrothorax.

COMMENT

It is doubtful whether anything which happened to this woman should be attributed to a neurological lesion incidental to this particular dissection. Any lay person is well enough qualified to judge of speech difficulties, but lay ideas about facial paralysis are very prone to be faulty. Nevertheless, this experience is at least suggestive. The autopsy protocol states: "A dissecting aneurysm of the aorta extends up to the horizontal part of the arch of the aorta." As pointed out by Crowell, there is need for more careful measurement of the mouths of the greater and lesser arteries which come off where aneurysmal dissection begins. Partial or complete closure of the great vessels to the head could produce cerebral ischemia readily.

SUMMARY AND CONCLUSIONS

1. Six cases of dissecting aortic aneurysm are reported, in five of which the diagnosis was confirmed at autopsy. In two instances it was possible to make a correct diagnosis before autopsy.

2. Wandering paralysis and vacillating sensory disturbances below the level of the umbilicus are stressed as very important diagnostic signs.

3. Spinal cord ischemia caused by interruption of an important source of blood supply directly from the aorta is discussed.

ADDENDUM

Among the articles which have appeared since this paper was submitted for publication, the following from the Massachusetts General Hospital¹³ deserves comment.

A 57-year-old woman with hypertension, four hours after sensation of smothering, showed "a gradually increasing pain and tingling in her right leg, soon followed by numbness, coldness, and paralysis of this extremity." There was "transient tingling in the right foot." Surgical search for an embolus in the subpopart portion of the right femoral artery was unsuccessful. The divided femoral vein bled freely from

above. At necropsy, aneurysmal dissection of the same type we have described was found to extend from a few centimeters above the aortic ring to the right external iliac, and 5 cm. above Poupart's ligament, where a fold of the intimal surfaces such as we have observed seemed to occlude the lumen.

The discussion by the clinicians failed to mention the paralytic symptoms, and they did not comment on the fact that "Two and a half hours after admission the patient could move her ankle but not the toes." We infer that the neurogenic factor was not considered.

Toomey¹⁴ has recently discussed the "segmental" character of the paretic and paralytic phenomena in poliomyelitis. His observations help explain both the vacillation and degree of the paralysis which we are discussing. He says, "Fibres from several segments run from the cord to several muscles in the periphery often in one large nerve." Thus he explains why there will be especial selectivity in the muscle groups afflicted; some from the same nerve will remain intact. The same factor seems to obtain in the segmental nutritional failure after aortic wall dissection.

REFERENCES

1. Herrick, James B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, *J. A. M. A.* 59: 2015, 1912.
2. Herrick, James B.: Thrombosis of the Coronary Arteries, *J. A. M. A.* 72: 387, 1919.
3. Hamman, Louis: Heart Pain of Organic Origin, *Internat. Clin.* 2: 157, 1935.
4. Hamman, Louis: Remarks on the Diagnosis of Coronary Occlusion, *Ann. Int. Med.* 8: 417, 1934.
5. Crowell, P. D.: Dissecting Aneurysms of Aorta: Report of Cases and Review of the Literature, *J. A. M. A.* 27: 2117, 1921.
6. Holland, Lang F., and Bayley, Robert H.: Dissecting Aneurysm, *AM. HEART J.* 20: 223, 1940.
7. Shennan, T.: Dissecting Aneurysms, *Med. Research Council Publications*, 1934, Special Report Series, 193; (3a) *ibid.*, 109; (3b) *ibid.*, 95; (3c) *ibid.*, 85; (3d) *ibid.*, 117.
8. Rogers, Hobart: Dissecting Aneurysm of the Aorta, *AM. HEART-J.* 18: 67, 1939.
9. Hirschboeck, F. J., and Boman, P. G.: A Case Report of Dissecting Aneurysm of the Aorta With Distinctive X-Ray Findings, *Minnesota Med.* 5: 724, 1922.
10. Galbraith, A. J., and Hardwick, S. W.: Spontaneous Rupture of the Aorta, *AM. HEART J.* 19: 100, 1940.
11. Resnik, W. H., and Keefer, C. S.: Dissecting Aneurysm With Signs of Aortic Insufficiency, *J. A. M. A.* 85: 422, 1925.
12. Letulle, M.: Anévrysme, disséquant étendu à la totalité de l'aorte et spontanément guéri; signes d'insuffisance aortique avec intégrité parfaite des valvules sigmoïdes, *Bull. et mém. Soc. méd. d. hôp. de Paris* 22: 1045, 1905.
13. Mallory, Tracy B. (Editor): Case Records of the Massachusetts General Hospital, *New England J. Med.* 225: 116, 1941.
14. Toomey, John A.: Diagnosis in Poliomyelitis, *J. A. M. A.* 117: 269, 1941.

THE EFFECT OF CHRONIC CARDIAC COMPRESSION ON THE SIZE OF THE HEART MUSCLE FIBERS

JOSEPH T. ROBERTS, M.D., PH.D.,* AND CLAUDE S. BECK, M.D.,
CLEVELAND, OHIO

INTRODUCTION

CONSIDERABLE confusion exists concerning the status of the heart in the compression disorders (Pick's disease, constrictive pericarditis). Is the compressed heart of normal size, is it smaller than normal, or is it larger than normal? Is the pull upon adhesions a factor in producing failure of the heart? Should the pectoral muscle and bony precordium be removed as a separate and distinct part of the operation for the cure of Pick's disease? Such a prominent surgeon as Schmieden¹ recommended removal of the pectoral muscle and the bony precordium, together with excision of the adherent scar. Schmieden's view was supported by Sauerbruch,² Winkelbauer,³ Westermann,⁴ Volhard,⁵ and Fischer.⁶ Throughout the literature on this subject it is stated that adhesions disturb the circulation. To relieve the ill effects of adhesions to the diaphragm, Payne, Sauerbruch, Fischer, and Schmieden recommend that the diaphragm be paralyzed by cutting the phrenic nerve. As a result of experimental studies, Ochsner and Herrmann⁷ and Herrmann and Musser⁸ concluded that adhesive pericarditis embarrassed the heart. According to these investigators, adhesions produce enlargement and hypertrophy of the heart. The terms used to designate these disorders—Pick's disease, Concato's disease, adhesive pericarditis, constrictive pericarditis—do not add clarity to the subject. This is readily apparent in discussions on diagnosis. It would appear that we are dealing with two factors which produce circulatory failure, namely, compression and a pull on adhesions.

The Pick syndrome was produced experimentally for the first time by Beck,⁹ in 1928. The development of the syndrome was incidental to a study of the action of a surgical solution of chlorinated soda (Dakin's solution) in the pericardial cavity. The study was undertaken to ascertain whether or not this solution could be used safely in the treatment of purulent pericarditis. After it was noted that cardiac adhesions and ascites followed the application of this solution to the pericardial cavity, it became apparent that a method was at hand to produce the Pick syndrome in animals. Beck and Griswold,¹⁰ using this method,

From the Departments of Medicine and Surgery of the Western Reserve University School of Medicine and the University Hospitals.

Aided by a grant from the Josiah Macy, Jr., Foundation.

Presented before the Society for Experimental Biology and Medicine, Cleveland, Ohio, April 14, 1939.

Received for publication Nov. 22, 1940.

*Rees Research Fellow in Medicine, now in Galveston, Texas.

carried out a study in which two observations of some importance to our subject and not in the literature at that time were made. One was that the Pick syndrome could be produced without any cardiac adhesions. The other was that, when the Pick syndrome developed, the heart became smaller than normal and that, when the pericardial scar was excised, the heart subsequently became of normal size. These measurements were made on standardized roentgenograms of the heart. The scar around the heart adds a certain amount to the roentgenographic shadow, and it is sometimes impossible to ascertain the size of the heart with any degree of precision because one cannot tell what part is scar and what part is heart. Because of this it is stated by several authors that the heart in this disorder can be small, normal, or large. In an analysis of the roentgenograms of twenty-six of our patients with compression caused by scars, Freedman¹¹ found that the cardiopericardial shadow was normal in size or smaller than normal in eighteen cases, moderately enlarged in six, and greatly enlarged in two. The heart shadow and the cardiopericardial shadow in this disease are not the same thing. It may be difficult or impossible to ascertain the exact weights of the hearts of patients who die from pericardial disease because the scar must be dissected from the heart before the organ is weighed. We know of no data on this subject, and a ratio between heart weight and body weight cannot be given. Even if such data were available, the patient's edema would disturb the ratio.

Fortunately the presence of atrophy or hypertrophy of the heart can be established by measurements of individual muscle fibers without knowing the exact weight of the heart. There is a perfect, positive, straight-line correlation between the size of the heart and the diameter of the fibers. This exact correlation (correlation coefficient = plus 0.872 [\pm 0.019]) was discovered by Roberts and Wearn¹² in a recent study of the capillary supply of the human heart during hypertrophy and growth. A similar study was carried out on rabbits by Shipley, Shipley, and Wearn.¹³ The method of these workers was used in the investigation reported here.

MEASUREMENTS

Five human hearts were available for study. Each of the patients from whom the specimens were obtained had had a severe degree of cardiac failure, presumably as a result of pericardial disease. In each case the heart was everywhere adherent to the pericardium. The pericardium was thickened, and was adherent to the diaphragm, pleurae, and chest wall. These patients died after removal of the scar. The heart weights given are those which were obtained after careful resection of the scarred pericardium (Table I).

Four sections were taken from various regions of the right and left ventricles of each heart, and 100 adjacent fibers were measured in each

section. Two diameters of each transversely cut fiber were measured with a calibrated ocular micrometer. In Fig. 1 the small muscle fibers of a compressed human heart are contrasted with the fibers of a normal and a hypertrophied heart. The mean fiber diameters in the five human hearts were 8.1, 8.9, 10.1, 11.2, and 11.2 microns. The average of the five mean measurements was 9.9 microns. In a study of twenty-six adult, normal, human hearts Roberts and Wearn¹³ found that the average mean fiber diameter was 13.9 (± 0.18) microns. The methods of measurement were the same in both studies. It can be seen that the largest fiber diameter in the group of five hearts from cases of pericardial disease and cardiac failure was less than the average normal. The average reduction in fiber diameter in the group of compressed hearts was 27.2 per cent of the normal value. The mean fiber diameter and the heart weights in these five cases of pericardial compression are plotted against each other in Fig. 2. This is a reproduction of the graph showing a positive correlation between heart weight and fiber diameter in children's and adults' hearts, taken from the paper of Roberts and Wearn,¹² with the addition of these five compressed hearts.*

TABLE I

CASE	FIBER DIAMETER (μ)	HEART WEIGHT (GM.)	HEART WEIGHT: BODY WEIGHT
<i>Human</i>			
1	8.1	175	0.00530
2	8.9	210	0.00295
3	10.1	360	0.00465
4	11.2	240	0.00381
5	11.2	280	0.00538
Av.	9.9	253	0.00442
Normal (Roberts and Wearn)	13.9 (± 0.18)	311 (± 7.42)	0.00543
<i>Dog</i>			
1	11.8	80	0.00666
2	12.6	75	0.00577
3	14.5	84	0.00600
Av.	12.9	80	0.00614
Normal (Mean of 6)	18.5	128	0.00827

An experimental study was made on eleven dogs. Constricting bands of linen tape were placed around the heart on the outside of the parietal pericardium. In several experiments the tapes were tightened at repeated operations at intervals of several months. In three of the experiments severe circulatory failure developed slowly over a period of about a year. The signs of circulatory failure consisted of ascites, high pressure in the jugular veins, subcutaneous edema, enlargement and frosting of the liver, distant heart sounds, and reduction

*In the graph these five compressed hearts are seen to fall well below the probable error of values for heart weight as predicted from the regression line (middle line) correlating heart weight and fiber diameter; this line, determined by Roberts and Wearn, has the formula: Fiber diameter $\pm 1.51 \mu = 8.22 + (0.0199 \times \text{heart weight})$.

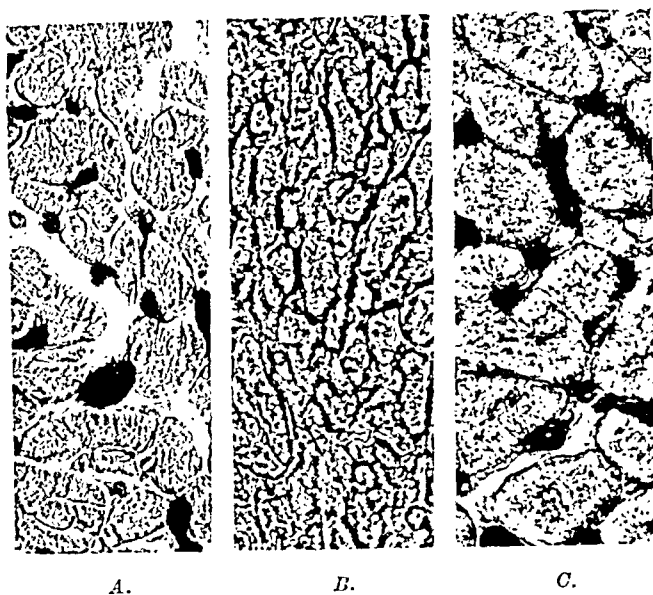


Fig. 1.—Photomicrographs of transversely sectioned, adult, human, cardiac muscle fibers. *A*, Normal; *B*, compressed heart of adhesive pericarditis; *C*, hypertrophied heart of syphilitic aortic insufficiency ($\times 500$).

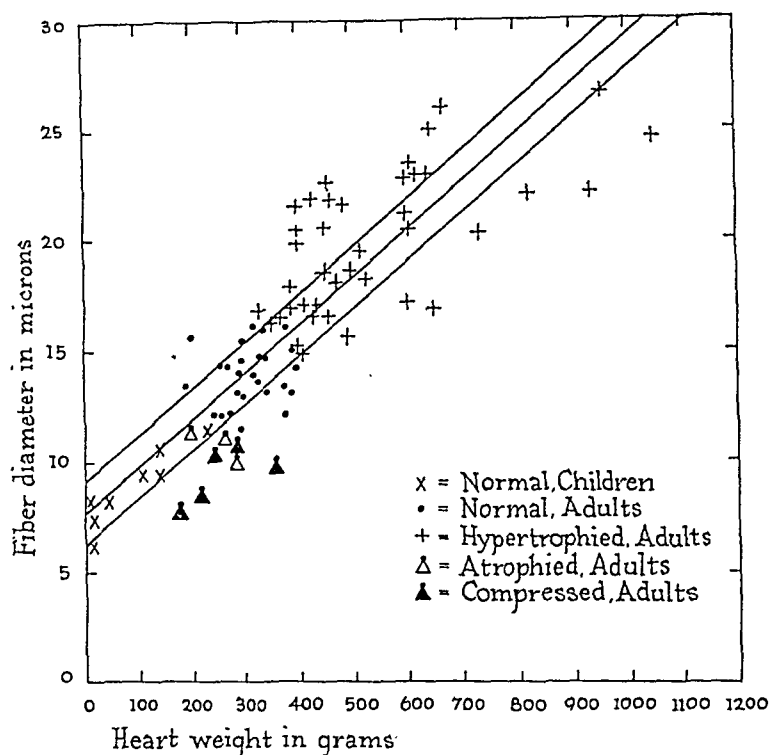


Fig. 2.—Chart correlating the heart weight and fiber diameter (human). The five hearts which had been chronically compressed by pericardial adhesions were smaller and had smaller fibers than the normal hearts studied by Roberts and Wearn.¹² The middle line is the regression line for fiber diameter from heart weight, and the upper and lower lines represent the range of the probable error for predicted values, as determined for the other noncompressed hearts shown here.

in the amplitude of the pulsations of the heart. When these animals were sacrificed, the tapes were found to be compressing the ventricles. Adhesions to the pleurae and mediastinum obscured the tapes. There were also some adhesions between the heart and parietal pericardium. The mean fiber diameters in these three dog hearts were 11.8, 12.6, and 14.5 microns. The average was 12.9 microns. A similar study on six normal, adult, dog hearts showed that the mean diameter was 18.5 microns. According to these measurements, the fiber diameter was reduced by about 30 per cent of the normal value. Table I summarizes the results of the study.

In both the human hearts and the experimental specimens there was a marked tendency toward uniformity in the size of the small fibers. This is in agreement with the observations of Karsner, Saphir, and Todd,¹⁴ who found that in the cardiac atrophy of chronic wasting disease the variability in fiber size which is characteristic of the normal heart is replaced by a uniform diminution in the size of the larger fibers. Also, the small fibers tended to be circular in cross section, rather than somewhat elliptical.

COMMENT

Each heart in which the fiber diameters were measured was compressed over a period of months or years. Adhesions between the heart and pericardium and between the pericardium and diaphragm, pleurae, and chest wall were present. Every specimen showed atrophy of the muscle fibers, and none showed hypertrophy of the muscle fibers. The presence of atrophy and the absence of hypertrophy in the individual muscle fibers signifies the presence of atrophy and the absence of hypertrophy in the entire heart. It appears, then, that cardiac compression produces cardiac atrophy and that adhesions do not produce hypertrophy of the compressed heart. According to the observations of Hosler and Williams,¹⁵ adhesions do not produce hypertrophy of the heart in the absence of valvular disease or hypertension, either in experimental animals or in human beings.

If the results of this study can be applied to compressed hearts in general, we can say that adhesions that do not compress the heart can be disregarded as a possible cause of failure in cases of compression. We can say also that there is no indication for removing the bony precordium or for paralyzing the diaphragm in the surgical treatment of this condition. That this conclusion is correct is demonstrated by the results of operations on patients with compression. Thirty-seven patients were operated upon by Beck. These patients had cardiac compression, together with adhesions to the chest wall, diaphragm, pleurae, pericardium, and heart. The compression scar was dissected from the heart and excised. As little of the bony precordium was removed as possible. The pectoral muscle was not removed, and the

diaphragm was not paralyzed. Of these thirty-seven patients, twenty-five were completely free from ascites after the operation and may be regarded as cured. Two additional patients were improved, and seven died. Of the two patients who were only improved, one had invasion of the myocardium by the scar, so that the heart was the seat of both extrinsic and intrinsic disease, and a complete cure could not be expected. The other had reformation of calcium deposits around and in the myocardium. Of the seven patients who died, three had active tuberculosis of the pleurae and mediastinum, one had an epicardial scar, plus bloody fluid, and died of infection, two died of heart failure caused by acute dilatation of the atrophic heart, and one died of ventricular fibrillation during the operation. It is obvious that removing part of the chest wall and paralyzing the diaphragm could not improve these results.

That the compressed heart undergoes atrophy of disuse was demonstrated by the clinical course of many of these patients. In every instance the heart dilated as the scar was removed. In every instance the circulation showed immediate improvement. Not infrequently, however, some of the improvement was lost after a day or two. The subsequent improvement in many cases was gradual, extending over a period of weeks or months. This delay occurs, we think, because the recovery from the atrophy of disuse suffered by the heart muscle is gradual. One would expect the heart muscle to require as much time as skeletal muscle to recover from an atrophic state.

CONCLUSIONS

1. In a series of human and dog hearts that were chronically compressed, the muscle fibers were smaller than normal in each instance.
2. In the presence of cardiac compression there is no evidence to indicate that adhesions play any role in producing circulatory failure, and there is no evidence to justify operation on the bony precordium, pectoral muscle, or phrenic nerve of patients with adherent and compressed hearts.
3. The compressed heart undergoes atrophy of disuse.

REFERENCES

1. Schmieden, V., and Westermann, H. H.: Operative Management of Fibrous Constricting Pericarditis, *Surgery* 2: 350, 1937.
2. Sauerbruch, F.: *Die Chirurgie der Brustorgane*, Berlin, 1925, Julius Springer, vol. 2, p. 297.
3. Winkelbauer, A., and Schur, M.: Zur chirurgischen Therapie der adhäsiven Perikarditis, *Med. Klin.* 31: 1231, 1269, 1935.
4. Westermann, H. H.: Die Indikation zur Operation der Herzbeutelentzündung, *Klin. Wchnschr.* 18: 1237, 1939.
5. Vollhard and Schmieden: Ueber Erkennung und Behandlung der Unklammerung des Herzens durch schwierige Pericarditis, *Klin. Wchnschr.* 2: 1, 1923.
6. Fischer, H.: Technique of Decortication of Heart, *Arch. f. klin. Chir.* 189: 548, 1937.
7. Ochsner, A., and Herrmann, G. R.: Experimental Surgical Relief of Experimentally Produced Pericardial Adhesions, *Arch. Surg.* 18: 365, 1929.

8. Herrmann, G. R., and Musser, J. H.: Experimental Pericarditis, *AM. HEART J.* 4: 268, 1929, and *Tr. A. Am. Physicians* 42: 23, 1928.
9. Beck, C. S.: The Effect of Surgical Solution of Chlorinated Soda (Dakin's Solution) in the Pericardial Cavity, *Arch. Surg.* 18: 1659, 1929.
10. Beck, C. S., and Griswold, R. A.: Pericardiectomy in the Treatment of the Pick Syndrome; Experimental and Clinical Observations, *Arch. Surg.* 21: 1064, 1930.
11. Freedman, Eugene: Inflammatory Disease of the Pericardium, *Am. J. Roentgenol.* 42: 38, 1939.
12. (a) Roberts, J. T., and Wearn, J. T.: Quantitative Changes in the Capillary-Muscle Relationship in Human Hearts During Normal Growth and Hypertrophy, *AM. HEART J.* 21: 617, 1941.
(b) Roberts, J. T., Wearn, J. T., and Badal, J. J.: The Capillary-Muscle Ratio in Normal and Hypertrophied Human Hearts, *Proc. Soc. Exper. Biol. & Med.* 38: 322, 1938.
13. Shipley, R. A., Shipley, L. J., and Wearn, J. T.: The Capillary Supply in Normal and Hypertrophied Hearts of Rabbits, *J. Exper. Med.* 65: 29, 1937.
14. Karsner, H. T., Saphir, O., and Todd, T. W.: The State of the Cardiac Muscle in Hypertrophy and Atrophy, *Am. J. Path.* 1: 351, 1925.
15. Hosler, R. M., and Williams, J. E.: A Study of Cardiopericardial Adhesions, *J. Thoracic Surg.* 5: 629, 1936.

ERRORS IN MEASUREMENT OF THE P-R (P-Q) INTERVAL AND QRS DURATION IN THE ELECTROCARDIOGRAM

PAUL D. WHITE, M.D., C. EDWARD LEACH, M.D., AND
STEPHEN A. FOOTE, M.D.
BOSTON, MASS.

IN THE fall of 1938, two interesting cases which were encountered within a brief period of time called our attention to a common and significant error in the measurement of the P-R (P-Q) interval of the electrocardiogram that has as yet escaped notice in the literature except for a brief preliminary reference published by us in the Transactions of the American Society for Clinical Investigation for 1939.¹ Fuller details and a further study of this problem are presented herewith.

It has been long recognized that the P-R interval and QRS duration are not always uniform throughout all leads of the electrocardiogram. In any given instance it is known that not all leads are equally favorable for recording the various deflections. The P waves are often poorly marked in Leads I and III, and the QRS complexes, particularly in Lead III, are subject to considerable variation in form. Lead II, which represents the algebraic sum of Leads I and III, usually has well-marked deflections, and it has been used most often for measurements of the time intervals.

Possible reasons for a variation in time intervals have been inadequately studied, and in books on electrocardiography one finds little definite reference to methods of measuring these intervals. Many books do not discuss the matter at all, except to state that the P-R interval is that portion of the tracing from the beginning of the P wave to the beginning of the QRS complex. In most cases there is no statement regarding lack of uniformity in different leads. Vaquez and Laidlaw² do not say how the P-R interval should be measured, but give the normal duration as 0.15 to 0.18 second. Lewis³ says that the measurement should be made from the beginning of P to the beginning of the ventricular complex, and that, as a rule, R is chosen for the sake of uniformity, but Q may be used if it is thought desirable. Carter⁴ recommends measuring from the beginning of the P wave to the beginning of the first deflection of the QRS, whether the latter is an upstroke or a downstroke. He further states that all measurements of complexes should be made in the lead in which they are longest, which is usually Lead II, but that sometimes Lead I or Lead III gives information not available elsewhere. Pardee⁵ also mentions the variation in the recording of P and QRS, but states that the longest P-R interval in any lead will be the most nearly correct one. Ashman and Hull⁶ say that the QRS

From the Cardiac Laboratory of the Massachusetts General Hospital, Boston, Mass.
Presented, in part, before the New England Heart Association, November, 1939.
Received for publication Dec. 15, 1940.

should be measured in the lead in which it is widest. They do not, however, discuss the mechanism of its variation.

It had been our practice in the routine reading of electrocardiograms to accept the longest intervals for P-R and QRS as the correct ones in any given record. The two cases already referred to in the first paragraph of this paper indicated, however, the need for further study and standardization of measurements in electrocardiography. The first patient, a healthy man, aged 52 years, had applied for insurance and showed no abnormalities on examination except for a P-R interval of 0.21 second in Lead II. Upon close scrutiny it was apparent that the P-R intervals in Leads I and III were both 0.18 second. There was a small Q wave in Lead I and a small R wave in Lead III which just balanced each other in Lead II to make the first part of the QRS complex isoelectric, thus adding 0.03 second to the P-R interval and shortening the QRS complex by the same amount in Lead II. It was obvious in this case that Lead II was unfavorable for measurement of both P-R interval and QRS duration, and also that the longest P-R interval was not the correct one.

A few days later a second case was encountered; this patient was a woman, aged 55 years, with lower chest pain, gaseous distention, and nausea, who was suspected of having coronary disease, despite a negative physical examination, because she had a P-R interval of 0.21 second in Lead II. Scrutiny of Leads I and III, however, disclosed, as in the first case, P-R intervals within normal limits (0.18 second), with Q_1 balancing, and so neutralizing, R_3 (Fig. 1).

Because these two cases seemed to refute accepted opinions, our interest was aroused concerning the nature of variations in other cases, and in establishing, if possible, criteria for the correct measurement of P-R interval and QRS duration. Records similar to the first two were soon found in the course of routine work in the laboratory, and simultaneous leads were taken in such cases to ascertain definitely the time relationship of the deflections in the various leads. Accurate measurements made with the Lucas comparator confirmed the first impression in these cases, and since the point of variation in the value of P-R intervals and QRS durations was not always the same in each case, a measurement of the P-S duration was instituted as a further aid. Its value will be illustrated later.

It was soon apparent that there are several ways in which the time intervals may vary in the different leads. The balancing of Q_1 and R_3 in cases of left axis deviation (Fig. 1) is a common type. In cases of right axis deviation the reverse occurs, that is, balancing of R_1 and Q_3 (Fig. 2). Apparent shortening of the P-R interval, especially in Lead I, occurs because of the isoelectric beginning of the P wave (Fig. 3), but is of little importance, per se, because it does not influence the other leads. Shortening of the QRS interval alone results in Lead II through

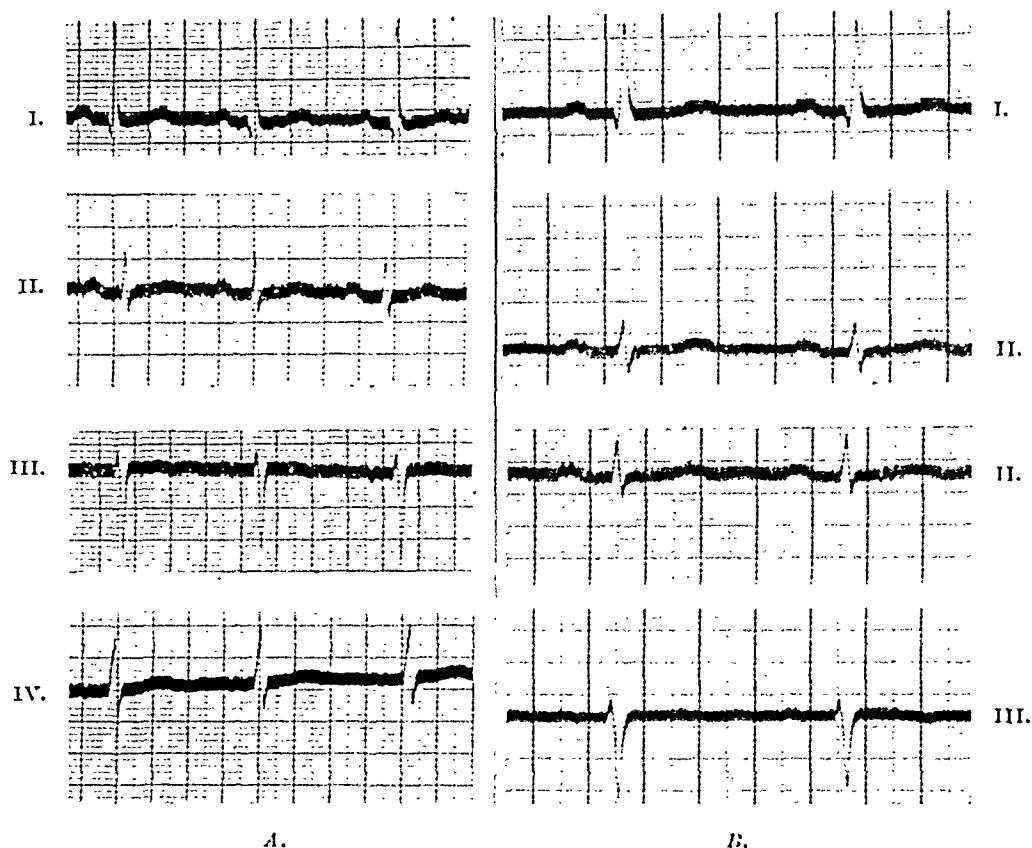


Fig. 1.—A. Routine Leads I, II, III, and IV. B. Simultaneous records of Leads I and II above, and of Leads II and III below. The small Q_1 and R_2 neutralize each other, to make the start of QRS_2 isoelectric. $P-R_2$ is longer and QRS_2 shorter than the corresponding intervals in Leads I and III. $P-R_1 = 0.18$ sec. $P-R_2 = 0.21$ sec. $P-R_3 = 0.18$ sec. Time = 0.2 and 0.1 sec. in this and in the following figures.

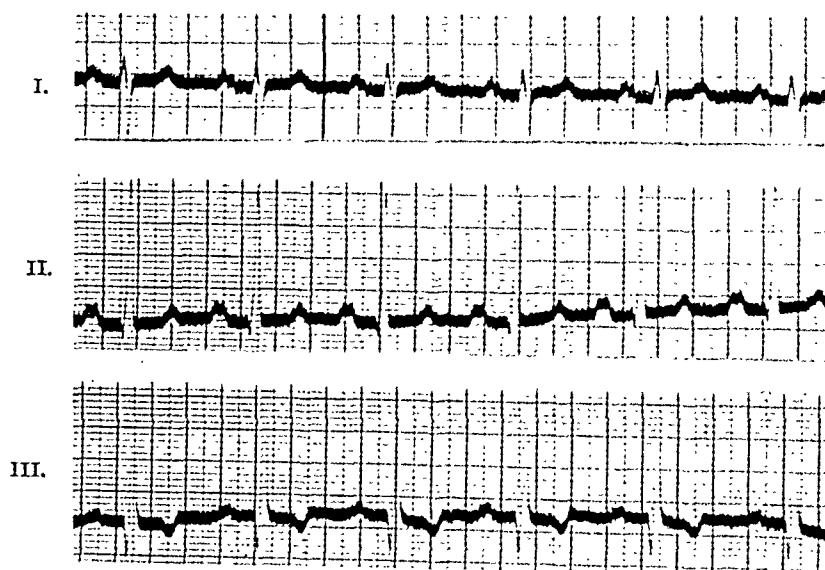


Fig. 2.—Routine Leads I, II, and III. Partial neutralization of R_1 and Q_2 produces an isoelectric beginning of QRS_2 . $P-R_1 = 0.20$ sec. $P-R_2 = 0.23$ sec. $P-R_3 = 0.21$ sec. Corresponding decrease in width of QRS_2 .

balancing of the S phases in Leads I and III, producing an isoelectric ending of QRS₂ (Figs. 4 and 5). It is seen in Figs. 4 and 5 that abnormal widening of the QRS waves would be overlooked if only Lead II were considered for measurement of the QRS, because the QRS duration is narrowed by isoelectric phases at both beginning and end. Fig. 6 illustrates the value of the P-S measurement. The QRS durations are different in all three of the standard leads, and the P-R interval in Lead I is shortened. The true P-R interval, as judged by the longest P-S duration minus the longest QRS duration, differs from all of the P-R intervals obtained by direct measurement. Apparently QRS in Lead II is narrowed by an isoelectric phase at the start, while QRS₃ is isoelectric at the end, and the P-R interval in Lead I is shortened by a late beginning of P.

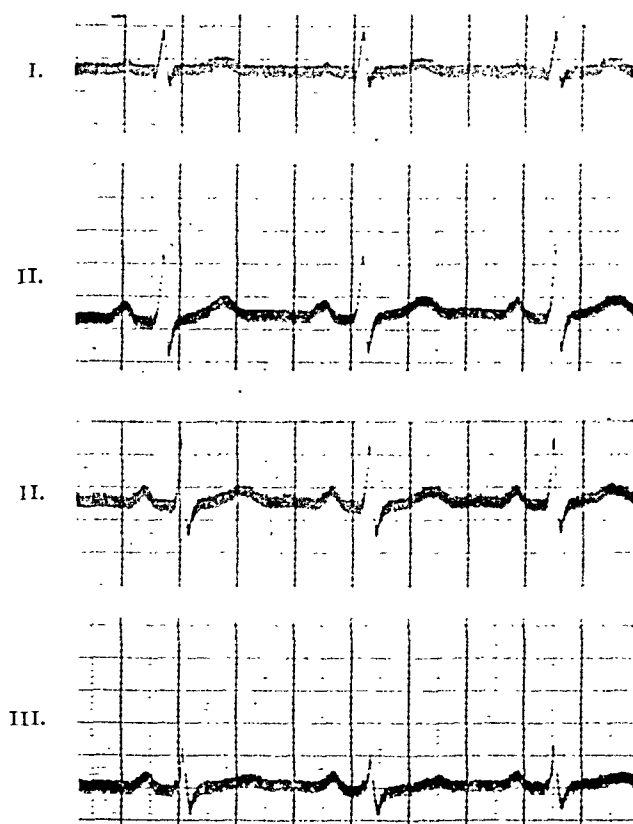


Fig. 3.—Simultaneous records of Leads I and II above, and of Leads II and III below. The isoelectric beginning of the P wave and the isoelectric ending of the QRS complex shorten both the P-R interval and the QRS duration in Lead I.

In order to get some idea of the incidence and possible importance of these variations in the time intervals, the electrocardiograms of 1000 consecutive patients were reviewed. A large number had a shorter P-R interval in Lead I only, and these were eliminated from consideration because, when Leads II and III agree, it is unlikely that any confusion could arise in arriving at the correct values. Thirty-eight tracings (3.8 per cent) were found to show significant variations (0.02 second or

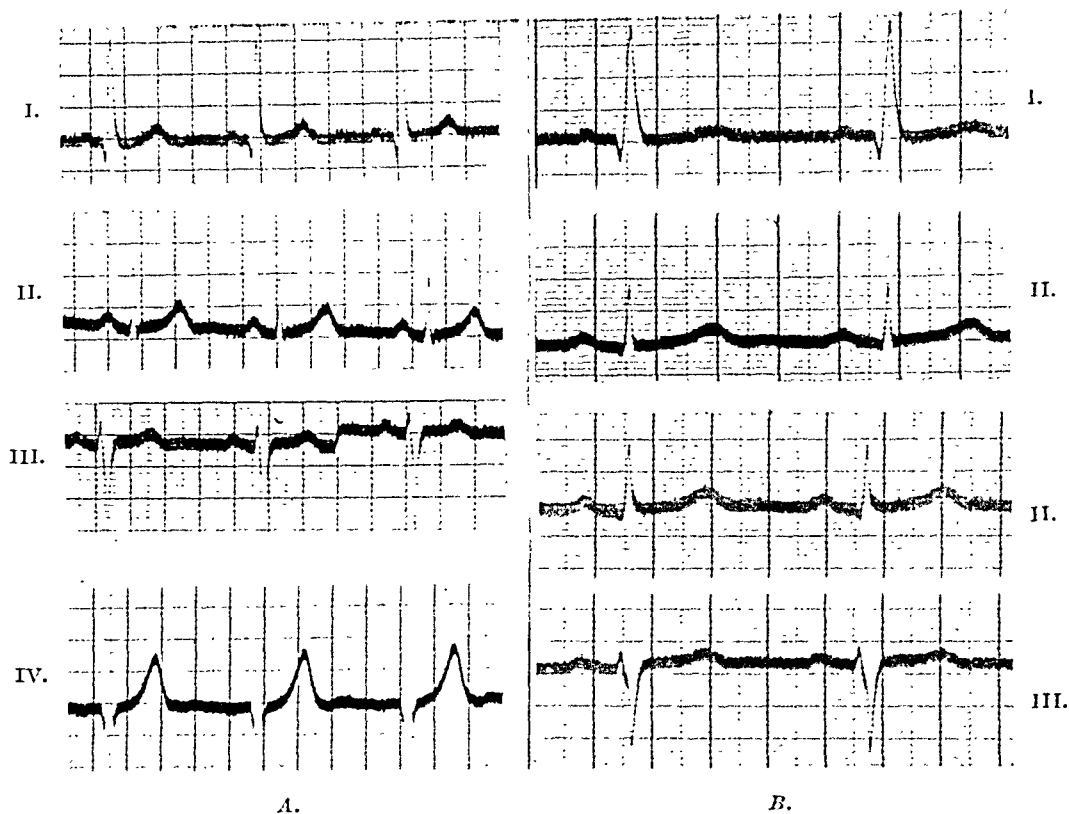


Fig. 4.—A. Routine Leads I, II, III, and IV. B. Simultaneous Leads I and II above, and Leads II and III below. QRS₂ shows isoelectric beginning and ending. Marked shortening of duration of QRS₂ as compared with these complexes in Leads I and III.

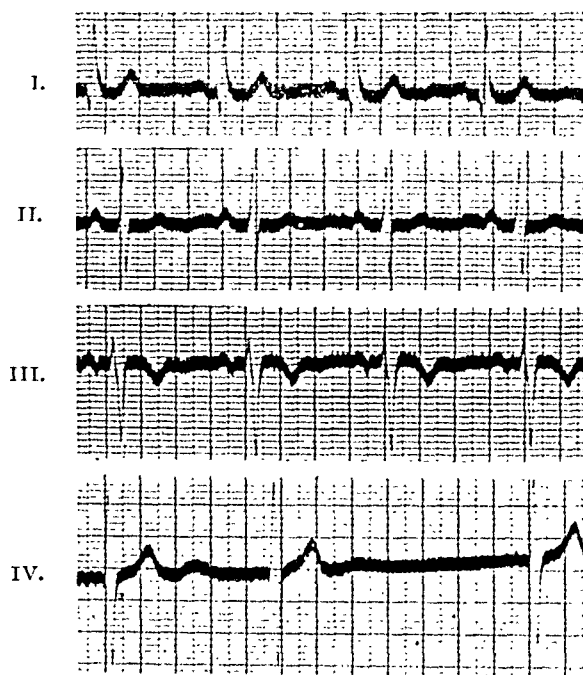


Fig. 5.—Routine Leads I, II, III, and IV. Small Q₁ and R₂ neutralize each other to lengthen the P-R interval and shorten the QRS duration in Lead II by 0.03 sec. The slightly prolonged intraventricular conduction time (0.11 sec. in Leads I and III) is not apparent in Lead II. QRS₂ = 0.08 sec.

more) in the duration of the P-R interval or QRS waves, or in leads other than Lead I. A variation in the P-R interval also was found in nine (0.9 per cent). Five patients (0.5 per cent) had differences in the QRS duration only. It was evident that in ten (1 per cent) of the cases the variations were clinically important, in that the short and long intervals straddled the dividing line between normal and abnormal, and because the determination of the correct values influenced the clinical diagnoses.



Fig. 6.—A. Routine Leads I, II, III, and IV. B. Simultaneous Leads I and III above, and Leads I and III below. Late beginning of P_1 , balancing of Q_1 , and isoelectric ending of QRS_2 make the time intervals differ in all three of the leads in the routine tracing (A). The true P-R interval, determined from the P-S (Lead II) minus the widest QRS (Lead I), equals 0.17 sec. and is different from any of the recorded P-R intervals. B, taken at a later date, illustrates well the isoelectric ending of QRS_2 .

The most common mechanism responsible for the disagreement between different leads was the balancing of Q_1 and R_3 in cases of axis deviation (thirty-one instances). The balancing of R_1 and R_3 was responsible in only three cases. Thirteen tracings showed isoelectric P waves, and four records had shortened P-R intervals in Lead I because the beginning of the P waves was isoelectric. In eight cases there was poor recording of the beginning of P_1 ; this was an infrequent observation in this group.

Of the thirty-three cases in which there were variations in P-R intervals, the longest P-R interval was incorrect in twenty-six and correct in seven. Lead II showed the correct P-R interval only six

in this group of thirty-three patients. In four instances the correct P-R interval, as ascertained from the P-S duration minus the longest QRS duration, differed from all of the recorded intervals. It is obvious that the QRS duration can err in only one direction, and that the longest one recorded must be most nearly correct. Contrary to the literature, however, Lead II did not prove to be the most reliable for this measurement. Of the twenty-nine patients with significant variations in QRS duration, with or without P-R interval discrepancies, not a single one had the correct value in Lead II. The apparent narrowing of the QRS waves is produced either by balancing of Q and R in Leads I and III, or by balancing of S phases, and this invariably affects Lead II, making the QRS complex narrower than it should be. It has already been shown (Figs. 4 and 5) to what extent this narrowing can occur.

Simultaneous registration of two leads affords the proof of these observations. However, in the absence of facilities for such registration it is still possible to decide with reasonable accuracy what are the correct P-R interval and QRS duration. At a glance it is evident whether Q_1 and R_3 or R_1 and Q_3 are about equal in amplitude and duration, whether the P is small and late, as it frequently is in Lead I, making the P-R interval too short in that lead, and whether the QRS is too narrow in one or more of the leads. One may obtain an approximately accurate P-R interval, without taking simultaneous leads, by subtracting the figure for the widest QRS wave from the longest P-S duration (that is, from the beginning of P to the end of S). In doubtful cases, Lead III is most likely to give the correct P-R interval. We have been able to prove the validity of these observations by the registration of simultaneous leads with our double string galvanometer, which has separate connections for each lead. Comparisons of the original tracings with those using simultaneous leads are shown.

The exact clinical significance of the observations reported here cannot be ascertained at once. However, since significant discrepancies in time relations occurred in about 3 per cent of the cases in our series, it is likely that these measurements will be of importance individually in an appreciable number of instances, either from the standpoint of insurance or diagnostically. The question also arises whether or not present standards of normal for P-R interval and QRS duration are actually correct. If normal standards for P-R intervals are based on measurements of the longest one in any lead, it is possible that our present upper normal limit has been fixed too high. We are not prepared to say at present whether an incidence of variation such as we have found would modify existing statistics or not.

Hill,^{7, 8} has recently gone back a little further to the fundamentals of differences in time relationships among the various leads in exploring the action currents over the chest wall. He also points out the occur-

rence of isoelectric phases in the complexes, with resultant discrepancies in measurements, and recommends observation of the intervals in all leads: he finds that if one P-R is different from the other two, the two that agree are correct, and if all three are different, the intermediate one is correct. Our results agree in most instances with his when we figure them according to his observations. However, we believe that the use of the P-S interval measurement is more reliable, for, in an occasional case (Fig. 6), direct measurement gives incorrect values from all three leads because of the presence of isoelectric phases (four cases in this series).

SUMMARY

1. We have discovered errors in existing methods of measurement of the P-R interval and QRS duration in the electrocardiogram.

2. These errors are usually the result of balancing of similar deflections of opposite direction in Leads I and III, producing isoelectric phases in Lead II. Lead II, therefore, is often the least reliable for the measurement of electrocardiographic time intervals.

3. Such variations were found to occur in 3.8 per cent of 1000 consecutive cases.

4. It is pointed out that the variations may be of considerable individual significance diagnostically, and may be of statistical importance from the standpoint of existing accepted values for normal limits of the P-R interval and QRS duration.

5. A simple method of avoiding the errors is presented. In general, Lead III has been found to be the most reliable single lead for the measurement of time intervals.

REFERENCES

1. White, P. D., Foote, S. A., and Leach, C. E.: A Common and Important Error in the Measurement of Auriculoventricular Conduction Time, *J. Clin. Invest.* 18: 489, 1939.
2. Vaguez, H., and Laidlaw, G. F.: *Diseases of the Heart*, W. B. Saunders Co., Philadelphia, 1924.
3. Lewis, Sir Thomas: *Clinical Electrocardiography*, Shaw & Sons, London, 1937.
4. Carter, J. B.: *The Fundamentals of Electrocardiographic Interpretation*, Charles C Thomas, Baltimore, 1937.
5. Pardee, H. E. B.: *Clinical Aspects of the Electrocardiogram*, Ed. 3, Paul Hoeber, New York, 1933.
6. Ashman, R., and Hull, E.: *Essentials of Electrocardiography*, Macmillan Company, New York, 1937.
7. Hill, A.: Analysis of the Normal QRS Waves, *Lancet* 2: 1115, 1938.
8. Hill, A.: Analysis of the Normal P Wave, *Lancet* 2: 415, 1939.
9. Willis, F. A.: *Clinical Electrocardiography*, W. B. Saunders Co., Philadelphia, 1922.
10. Barnes, A. R.: *Electrocardiographic Patterns*, Charles C Thomas, Baltimore, 1940.
11. Master, A. M.: *The Electrocardiogram and X-Ray Configuration of the Heart*, Lea and Febiger, Philadelphia, Pa., 1939.
12. Evans, W.: *A Students' Handbook of Clinical Electrocardiography*, H. K. Lewis & Co., Ltd., London, 1934.
13. Parsonnet, A. E., and Hyman, A. S.: *Applied Electrocardiography*, Macmillan Co., New York, 1929.
14. Schnitzer, M. A.: *The Electrocardiogram in Congenital Cardiac Disease*, Harvard University Press, Cambridge, 1940.

OBSERVATIONS ON REACTIVE HYPEREMIA IN VARIOUS PORTIONS OF THE EXTREMITIES

DAVID I. ABRAMSON, M.D., KURT H. KATZENSTEIN, M.D., AND
EUGENE B. FERRIS, JR., M.D.
CINCINNATI, OHIO

IN GENERAL, it can be stated that the functional needs of a tissue largely determine the rate of local blood flow. In any situation in which function is dependent upon local metabolism, it would follow that this latter factor should likewise play a role in controlling the rate of local blood flow. Insofar as the hand and fingers are concerned, however, marked and transient variations in flow have been reported. These variations obviously could not be related to changes in metabolism, and have been attributed, in part, to the fact that the hand, through the medium of its numerous arteriovenous shunts, performs an important function in the conservation and dissipation of body heat under ordinary environmental conditions.¹ Further, it has been shown that the vessels in the hand respond markedly to other types of stimulation.²⁻⁴ Since the transient alterations in flow produced by these various factors are dependent upon the integrity of the sympathetic nervous system,⁵ the vascular responses in the sympathectomized hand would be expected to be much more closely related to the metabolic needs of the tissues than are those in the innervated hand; this relationship was demonstrated recently by Freeman.⁶

A number of investigators, notably Bier,⁷ Moskowitz,⁸ Roy and Brown,⁹ Lewis and Grant,¹⁰ and Freeman,⁶ have studied the phenomenon of reactive hyperemia, which, in brief, designates the duration of increased blood flow to an extremity after a period of arterial occlusion. Some of these workers feel that, within certain limits, the subsequent increase in circulation is dependent upon the length of time that the tissues suffer from anoxia. According to Roy and Brown,⁹ the increased blood flow represents an attempt on the part of tissues which have been deprived of a proper blood supply to become repossessed of it. Since reactive hyperemia appears to be related to tissue metabolism, it was thought worth while to study this response in the innervated hand, in the forearm, and in the leg, in the hope that more information might be gained concerning the mechanism involved in the increased local blood flow in the different vascular beds.

From the May Institute for Medical Research of the Jewish Hospital, and the Department of Internal Medicine, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

Read before the American Physiological Society, New Orleans, March, 1940.

Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

Received for publication Dec. 21, 1940.

METHOD

The effect of varying periods of arterial occlusion on blood flow in the hand, forearm, and leg was studied in a series of forty-three normal subjects by means of the venous occlusion plethysmographic method. The sympathectomized extremities of a female patient (R. M.), with Raynaud's disease, were also tested. Generally, from two to five experiments were performed upon each subject. Blood flow readings were made simultaneously on two extremities which were exposed to a bath temperature (temperature of the water in the plethysmograph) of either 10° to 14°, 32°, or 45° C., at a room temperature of 25° to 27° C. In the case of the forearm and leg, pressures of 300 mm. Hg were maintained at the wrist and ankle during the period of blood flow measurements, so that vascular changes in the distal portions of the extremities could not influence the results.¹ The apparatus and technique used in obtaining and calculating the blood flow measurements were similar in all respects to those previously described.¹¹

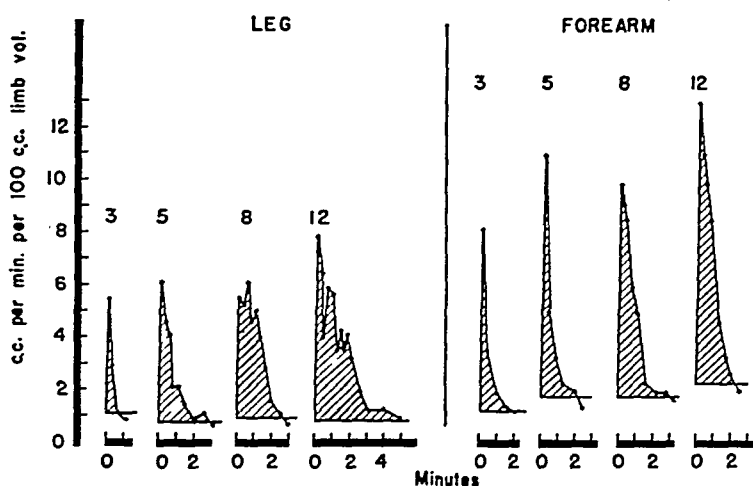


Fig. 1.—Effect of varying periods of arterial occlusion upon magnitude of total blood flow repayment. Leg (C. B.)—3 min. occlusion—1.5 c.c. total repayment; 5 min.—4.0 c.c.; 8 min.—6.4 c.c.; 12 min.—10.8 c.c. Forearm (L.S.)—3 min. occlusion—2.7 c.c. total repayment; 5 min.—4.0 c.c.; 8 min.—7.2 c.c.; 12 min.—10.8 c.c. Bath temp.—32° C.

After eight to ten control readings were obtained over a period of twenty to thirty minutes, reactive hyperemia was produced by suddenly applying an arterial occlusion pressure to the proximal portion of the limb by means of a blood pressure cuff connected to a pressure system. In the case of the forearm and hand, the cuff was generally applied to the arm just above the elbow, and of the leg, to the thigh above the knee. In a number of instances, reactive hyperemia was elicited in the hand by applying the cuff around the forearm. After different periods of application, ranging from three to twelve minutes, the pressure was released and blood flow readings were obtained at 10-second intervals for the first two minutes, and then at longer intervals for the next eight minutes. In some instances, the first measurement was recorded within a second after the onset of reactive hyperemia, according to the technique of Lewis and Grant.¹⁰

For each experiment a graph was constructed from the blood flow measurements (in c.c. per min. per 100 c.c. of limb vol.) which were obtained during the ten-minute interval after the release of the arterial occlusion pressure (Figs. 1 and 2). By means of a planimeter, the number of cubic centimeters of excess blood flow over and above the estimated control level was obtained for the period of reactive hyperemia. The basal flow during reactive hyperemia was ascertained by averaging a number of resting blood flow figures which were obtained before arterial

occlusion and after the effect of the occlusion had disappeared. Since different periods of arterial occlusion were used, it was necessary to express the number of cubic centimeters of excess blood flow as the actual repayment elicited by one minute of arterial occlusion for each 100 c.c. of limb volume. The percentage of blood flow "debt" which was repaid was calculated by dividing the repayment for one minute of occlusion by the theoretical "debt" incurred during this period of time. The latter figure was regarded as equal to the control blood flow per min. per 100 c.c. of limb volume, on the assumption that this quantity of blood would have ordinarily entered the limb during each minute of the experimental period if no occlusion pressure had been applied.

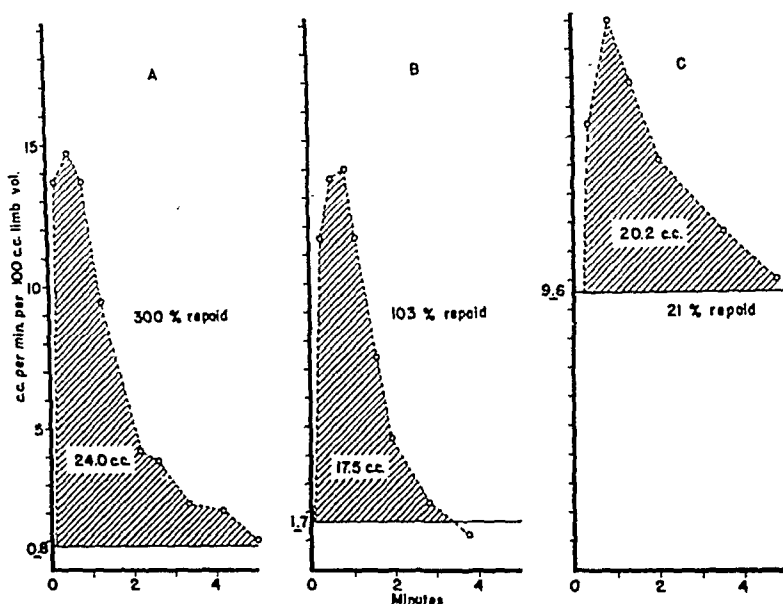


Fig. 2.—Hand. Effect of a ten-min. period of arterial occlusion in subjects J. S. (A), H. P. (B), and C. W. (C), with different control blood flow levels. Figures within graphs—total repayment over and above control blood flow levels. Theoretical "debt" incurred calculated by multiplying control blood flow by ten minutes. Bath temp.—32° C.

RESULTS

Comparison of type of response of the hand, forearm, and leg to arterial occlusion.—In the case of all three of these sites, the greatest augmentation of flow at the different bath temperatures took place within the first ninety seconds after removal of the arterial occlusion pressure. From that point on, the flow rapidly and progressively diminished, so that, after a ten-minute occlusion period, the curve representing blood flow generally returned to the control level in approximately three to four minutes after release of the pressure (Fig. 2). After shorter periods of occlusion, the contour of the initial portion of the graph (and, at times, its height also) remained unchanged, but the descending limb reached the control baseline somewhat sooner (Fig. 1). The range of maximal blood flow response in the different subjects extended over a period of five to twenty seconds after the release of the arterial occlusion pressure.

When the blood flow in the forearm and leg had returned to approximately the same level as the initial resting flow, the readings obtained

thereafter continued to fall within a narrow range on either side of the average control. In the hand, however, in approximately one-half of the cases in which the arterial occlusion pressure was applied for ten minutes or more, the flow, after a brief initial rise, dropped significantly below the control level for a short time, and then approached it again within three or four minutes (Fig. 3). Almost invariably this "negative phase" was associated with a painful feeling in the finger tips which could best be described as a "pins and needles" sensation. The decrease in flow was generally not observed in those subjects who had low control blood flow readings, even though the "pins and needles" sensation occurred. In the patient with a sympathectomized upper extremity (R. M.), the painful sensation was likewise not associated with a negative phase in the hand, although in this case a relatively normal flow was present.

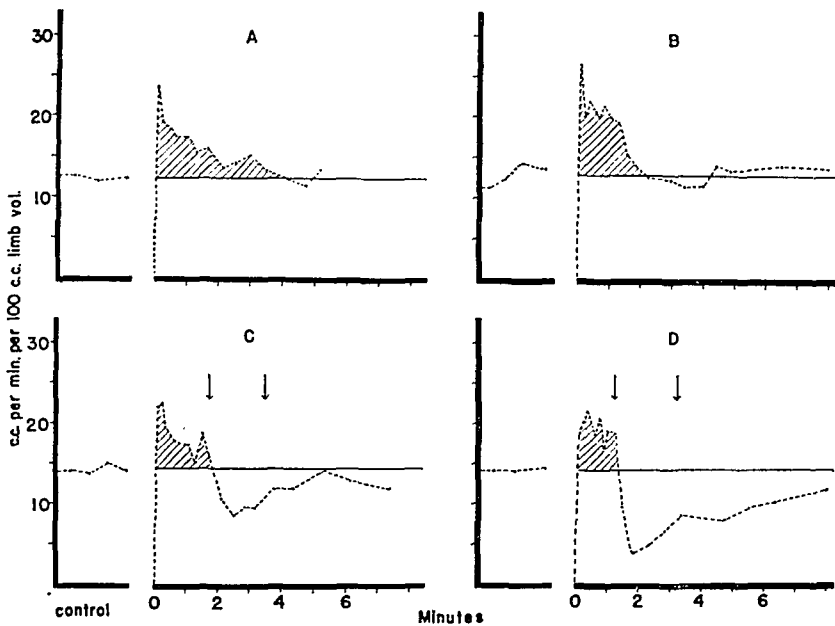


Fig. 3.—Hand. Relationship between negative phase and onset and duration of "pins and needles sensation" in fingers (indicated by period between arrows). Subject L. S. A and B—five and eight minutes of arterial occlusion (cuff on forearm)—no negative phase and no painful sensation. C and D—ten minutes of arterial occlusion to forearm and arm, respectively—definite negative phase and severe "pins and needles sensation" (more marked in D). Bath temp.—32° C.

It was deemed necessary at the outset to ascertain whether the decrease in flow in the hand was part of the phenomenon of reactive hyperemia, or whether it was merely a nonspecific response of the vessels of the hand to a noxious stimulus. In this connection it was noted that in those cases in which no "pins and needles" sensation was experienced (generally because the occlusion pressure was applied for a period of three or five minutes, instead of ten), there was usually an absence of the "negative phase" (Fig. 3 A and B). The reverse, as has already been stated, was also true; the painful stimulus was associated with a negative phase (Fig. 3 C and D) unless the control flow

was low (the only exception to this was the response in the sympathectomized hand). In those experiments in which blood flow determinations were made simultaneously on two hands, with production of reactive hyperemia in only one, a decrease in the resting blood flow in the control hand was observed at approximately the same time that the "pins and needles" sensation and the "negative phase" appeared in the other hand. Further, when both hands were subjected to arterial occlusion, the "negative phase" was always more marked in each than when the arteries to only one were occluded. In addition, the pain experienced by the subject as a result of "pins and needles" sensation in the fingers of both hands was more intense.

At this point it is necessary to emphasize the fact that the forearm and leg rarely, if at all, showed a "negative phase" during the period of reactive hyperemia (Fig. 1). Such dissimilar behavior of the hand, as compared with the forearm and leg, is in accord with the observations of previous workers on the responses of the blood vessels in these sites to noxious stimuli.⁴ The above results, together with the fact that a "negative phase" was not observed in the sympathectomized hand, would support the view that this decrease in flow which is frequently present in the normally innervated hand during a period of reactive hyperemia is caused by increased sympathetic tonus resulting from the associated painful sensation. Accordingly, curves from the hand in which there was a "negative phase" have not been included in the results.

Reactive hyperemia at different bath temperatures.—Since at a bath temperature of 32° C. (which is approximately equivalent to normal skin temperature) and at a room temperature of 25° C. there is neither excessive constriction nor excessive dilatation of either skin or muscle vessels, it was possible to study reactive hyperemia in a physiologic state. Examination of Table I reveals that under these conditions the actual blood flow repayment which was elicited by a minute of arterial occlusion was greatest in the hand, somewhat less in the forearm, and least in the leg. It is of interest that the repayment in the different portions of the sympathectomized extremity was grossly similar to that in the normally innervated limb (Table I).

With the extremity exposed to a high bath temperature (43° C.), reactive hyperemia could be studied during a period in which maximal dilatation of cutaneous vessels had already taken place; the muscle vessels were probably not significantly affected by such a procedure. It would follow, therefore, that during reactive hyperemia at the high bath temperature the increased flow is due principally to dilatation of blood vessels in the muscle.

Most of these experiments were performed upon the forearm; the severe pain experienced during the period of occlusion at the high bath temperature made it impractical to utilize the hand, in view of

TABLE I
EFFECT OF DIFFERENT BATH TEMPERATURES ON REACTIVE HYPEREMIA

SUBJECT	FOREARM			LEG			HAND	
	CONTROL FLOW	REPAYMENT ON BASIS OF 1 MIN. OCCLUSION	SUBJECT	CONTROL FLOW	REPAYMENT ON BASIS OF 1 MIN. OCCLUSION	SUBJECT	CONTROL FLOW	REPAYMENT ON BASIS OF 1 MIN. OCCLUSION
BATH TEMPERATURE—10° TO 14° C.								
E. F.	0.9	0.6	K. K.	1.2	0.5	J. K.	4.7	0.5
L. S.	0.7	0.5	J. K.	1.5	0.7	J. A.	0.3	0.1
M. K.	0.5	0.4	J. A.	0.4	0.2	C. S.	0.3	0.6
D. A.	1.0	0.9	E. A.	1.4	0.3	K. K.	2.2	0.5
L. B.	0.5	0.4	M. T.	1.4	0.8	D. A.	1.4	0.5
						S. F.	4.2	0.4
						L. S.	4.6	0.2
Av.	0.7	0.5	Av.	1.2	0.5	Av.	2.5	0.4

BATH TEMPERATURE—32° C.									
R. J.	1.7	1.5	A. H.	1.1	1.0	E. M.	8.0	3.5	
K. K.	1.9	2.3	B. P.	0.9	0.9	P. M.	6.1	2.1	
E. M.	2.7	1.3	R. W.	1.0	1.0	E. G.	5.3	3.9	
E. G.	0.8	1.5	K. K.	1.5	1.6	D. A.	6.0	2.1	
P. M.	2.4	1.5	D. A.	1.4	0.5	P. D.	5.1	1.2	
D. G.	1.6	2.0	H. F.	2.6	0.9	D. G.	5.1	1.9	
M. M.	1.1	1.1	L. S.	1.1	0.5	M. M.	6.7	1.0	
N. R.	1.5	1.7	W. A.	1.7	1.1	J. R.	10.1	1.3	
H. S.	0.9	1.6	E. A.	1.7	0.5	L. S.	10.5	1.5	
J. R.	2.1	1.6	S. S.	1.5	0.6	C. T.	2.5	2.2	
E. L.	1.6	1.1	J. L.	1.5	0.5	F. B.	7.9	1.5	
D. A.	1.6	1.3	T. M.	1.1	0.6	L. B.	6.0	2.7	
L. P.	1.1	1.8	J. Z.	1.2	0.8	M. A.	3.5	1.4	
M. K.	1.0	1.4	D. A.	1.5	0.6	J. Z.	5.9	1.2	
L. S.	1.6	1.1	M. L.	1.5	1.0	J. S.	6.8	2.4	
C. P.	1.2	1.2	S. F.	0.8	0.3	C. W.	9.6	2.0	
C. T.	2.0	1.9	C. B.	0.9	0.8	H. P.	1.7	1.8	
C. D.	1.8	1.4	S. L.	1.0	0.5	R. M.	6.8	1.3*	
A. F.	2.0	1.3	S. J.	2.2	0.7				
F. B.	1.1	1.2	R. M.	2.2	0.9*				
M. A.	1.7	1.6							
O. H.	1.0	1.0							
R. M.	2.1	0.9*							
Av.	1.5	1.5	Av.	1.1	0.8	Av.	5.8	2.0	
BATH TEMPERATURE—43° C.									
P. M.	9.3	2.0							
R. J.	6.0	1.2							
M. S.	10.5	2.2							
J. R.	7.8	1.3							
D. A.	5.1	2.1							
C. T.	8.7	0.8							
Av.	7.9	1.6							

All control flow readings in c.c. per min. per 100 c.c. blood vol.

*Sympathetomized extremities.

the known effect of noxious stimuli upon the blood vessels of the hand.²⁻⁴ Examination of Table I reveals that the blood flow repayment per minute of arterial occlusion in the forearm was approximately the same at the high bath temperature as at a temperature of 32° C. In the few instances in which the leg was subjected to the same procedure (results not included in the table), the results were similar to those in the forearm.

At the low bath temperature (10° to 14° C.), an opportunity was afforded to study reactive hyperemia during a period in which the blood flow through the cutaneous blood vessels was markedly diminished as a result of the constricting effect of cold. Since the cold does not penetrate to any significant extent below the skin layer,¹² it may be assumed that the resting blood flow figures obtained for the forearm and leg at the low bath temperature represented muscle blood flow primarily. In the case of the hand, however, the possibility existed that in some instances not all of the arteriovenous shunts were entirely closed by the stimulus, with the result that the control flow still included some flow through these vessels. In fact, in some subjects, even when the bath temperature was lowered to 8° or 10° C., the hand flow still remained somewhat elevated. In respect to reactive hyperemia, however, the blood flow repayment elicited by a one-minute period of arterial occlusion in these latter cases was approximately the same as in those in which the control flow was low. Further, the average repayment for the hand, forearm, and leg was also grossly similar. It is of interest that, for at least the hand and forearm, this figure was significantly less at the low bath temperature than that obtained by the same procedure at 32° C. (Table I).

Comparison between the maximal blood flow in response to arterial occlusion and that elicited by direct heat.—In forty-two experiments the resting blood flow of the limb at a bath temperature of 43° C. was compared with the maximal blood flow after a ten-minute period of arterial occlusion at a bath temperature of 32° C. In the hand, the average control blood flow at a bath temperature of 43° C. was 28.2 c.c. per min. per 100 c.c. of limb volume, whereas the greatest flow recorded during a period of reactive hyperemia, at a bath temperature of 32° C., averaged 19.3 c.c. In the forearm the reverse was true; the average control blood flow at the high bath temperature was 7.9 c.c., whereas arterial occlusion at a bath temperature of 32° C. elicited a maximal response which averaged 12.7 c.c. Likewise in the leg, the latter relationship was present; the average control flow at 43° C. was 3.3 c.c., and the greatest flow during reactive hyperemia at 32° C. averaged 7.2 c.c.

DISCUSSION

It is generally held that in normal subjects the magnitude of the hyperemic response which follows deprivation of blood flow is related

to the metabolic needs of the tissues involved. The observations here reported are consistent with such a view when the known facts concerning the regulation of blood flow to the various regions studied are considered. For example, as previously stated, the blood vessels of the hand, in addition to supplying the metabolic needs of the tissues, also function to dissipate heat¹ and possibly to regulate circulating blood volume.¹³ Since the function of heat dissipation is active in the hand at ordinary local and environmental temperatures, it would be expected that the control resting flow would be much greater than the amount necessary for metabolic purposes. This is substantiated by our observations, for the blood flow repayment per minute of arterial occlusion at a bath temperature of 32° C. was much less than the theoretical "debt" incurred (equal to control flow per minute). Actually, if the cases in which a negative phase occurred had been included in the series, the average repayment in the hand would have been even less. At extremely low bath temperatures, the resting flow in the hand was in some instances of the same order of magnitude as that in the forearm and leg, and, during reactive hyperemia, the repayment approximately equalled the control flow per minute and, hence, the blood flow "debt" (Table I). In these cases it would appear that the hand was no longer serving the function of heat dissipation, and that its blood flow was dependent chiefly upon metabolic needs.

In the forearm, at bath temperatures of 14° and 32° C., the control flow was quite constant in the same and in different subjects, and the magnitude of the repayment per minute of arterial occlusion approached that of the blood flow "debt" (Table I). Previous studies have demonstrated that, at such local and environmental temperatures, the arterioles in this region are not influenced by sympathetic tonus and are not concerned directly in the process of heat dissipation.^{4, 13} The fact that the repayment and the blood flow "debt" were equivalent would suggest that, under these circumstances, the resting flow was dependent chiefly upon the metabolic needs of the tissues. At a bath temperature of 43° C., however, the relation of the resting flow in the forearm to the amount repaid was entirely different; it resembled more closely the response in the hand at 32° C., in that only a small percentage of the "debt" was repaid (Table I). A similar type of response in the forearm has also been obtained by producing extreme degrees of reflex vasodilatation through the application of heat to distant portions of the body.¹³ Under these circumstances the forearm was serving the function of heat dissipation, even at a bath temperature of 32° C., and, as would be anticipated, arterial occlusion resulted in a repayment of only a small percentage of the theoretical blood flow "debt." Further evidence was obtained by comparing the resting flows in the forearm at 14°, 32°, and 43° C. (Table I). Those obtained at 43° C. were considerably higher than would be expected as a result purely of increased

TABLE II
EFFECT OF VARYING PERIODS OF OCCLUSION—BATH TEMPERATURE, 32° C.

FOREARM				LEG				HAND			
SUBJECT	CONTROL FLOW	PERIOD OF OCCLUSION MIN.	REPAYMENT ON BASIS OF 1 MIN. OCCLUSION C.C.	SUBJECT	CONTROL FLOW	PERIOD OF OCCLUSION MIN.	REPAYMENT ON BASIS OF 1 MIN. OCCLUSION C.C.	SUBJECT	CONTROL FLOW	PERIOD OF OCCLUSION MIN.	REPAYMENT ON BASIS OF 1 MIN. OCCLUSION C.C.
C. T.	1.7 2.3	3 5	1.8 1.9	S. L.	1.1 0.9 0.9	5 8 10	0.4 0.5 0.5	L. S.	14.2 12.9 12.8	3 5 8	2.6 1.6 1.6
F. B.	1.1 1.1	3 5	0.8 1.6	K. K.	1.6 1.2 1.4	3 5 10	0.8 1.1 0.9	S. L.	10.7 12.3	3 5	3.5 3.4
M. A.	1.6 2.1 1.5	3 5 5	1.8 1.3 1.7	L. S.	1.1 1.0 1.2	3 5 8	0.5 0.7 0.5	C. B.	6.1 5.1 4.5	5 8 12	1.6 1.8 1.4
C. P.	1.4 1.1	5 10	1.2 1.3	E. A.	1.7 1.7	5 8	0.8 0.6	S. S.	5.8 5.7 5.1	3 5 8	2.1 1.1 1.1
L. S.	1.4 1.7 1.7 1.9 2.3	3 5 8 10 12	0.9 0.8 0.9 0.9 0.9	T. M.	1.1 1.1 1.1	3 5 7	0.6 0.6 0.4	C. T.	2.3 2.6	3 5	2.2 2.1
R. J.	1.6 1.9 1.6	5 8 10	1.6 1.2 1.7	J. Z.	1.2 1.2	3 5	1.0 0.8	L. B.	7.9 7.9	3 5	1.7 1.3
S. S.	1.1 1.2 1.2	3 5 8	1.2 1.0 1.0	R. M.	2.3 2.2	5 8	0.9 1.0	M. A.	3.8 3.6 3.0	3 5 8	1.2 1.8 1.1
R. M.*	2.3 2.0	5 8	0.9 0.9	C. B.	1.1 0.8 0.9 0.9	3 5 8 12	0.5 0.8 0.8 0.9	J. Z.	6.6 5.5	3 5	1.2 1.3
				S. J.	2.5 2.0	3 5	0.8 0.7	R. M.*	5.8 4.9	5 8	1.5 1.3

Control flow in c.c. per min. per 100 c.c. limb vol.

*Sympathectomized extremities.

metabolism caused by heat. It would then appear that, at high bath temperatures, the total blood flow to the forearm is dependent on factors other than local metabolic needs, whereas, at the lower bath temperatures, a definite correlation exists between the resting blood flow and the metabolic requirements of the tissues.

Further evidence for the view that the blood flow repayment is related to the metabolism of the tissue was obtained by varying the duration of arterial occlusion. In the forearm and leg, and, under certain conditions, in the hand, the magnitude of the repayment was found to be directly proportional to the blood flow "debt" which was incurred (Table II, Fig. 1). This relationship existed for all three bath temperatures. Of course, it must be borne in mind that a blood flow "debt" may be repaid not only by a more rapid rate of blood flow, but also by a greater removal of metabolic products from each 100 c.c. of blood during its passage through the tissues. As a result, a direct relationship between the magnitude of the blood flow "debt" which is incurred and the subsequent increase in blood flow might not always be realized. This may explain some of the results which appear at variance with the majority of the observations (Table II).

It has been found that the magnitude of the first few blood flow levels after release of arterial occlusion is quite independent of the total repayment. This lack of correlation is evident not only in comparing the observations on different subjects, but also on the same subject, after varying periods of arterial occlusion. In some instances the maximal height of the initial blood flow readings after five minutes of occlusion was approximately the same as that after eight or ten minutes; the total number of cubic centimeters of excess blood flow was, of course, smaller for the shorter period (Fig. 1). Such evidence would suggest that the use of the maximum blood flow response during reactive hyperemia as a comparative index of the total response is not justified. Since variations in the shape of the blood flow curve during reactive hyperemia are such that, from a given point in the graph, neither the height of the maximum response nor the amount of the total response can be predicted (Figs. 1 and 2), the procedure of obtaining a single reading at an arbitrarily fixed time after the release of the arterial occlusion pressure¹⁰ is also open to criticism. On the other hand, by obtaining frequent blood flow readings, particularly during the initial portion of the period of reactive hyperemia, one is able to ascertain the maximal blood flow response to a given stimulus, and thus obtain an index of the degree of arteriolar dilatation. In this respect the use of the term "actual blood flow repayment per minute of arterial occlusion" apparently has more significance than "percentage of blood flow debt repaid." This is clearly demonstrated in Fig. 2, in which the repayment for a ten-minute period of occlusion in the hand is recorded in the case of three subjects with varying control blood flow levels. Although the actual repayment

was approximately the same in all three cases, the percentage repayment varied markedly because of the differences in theoretical blood flow "debt"; the latter was derived from the control resting blood flow. Further, in the case of the forearm and leg, because of the relatively low control blood flow readings, very slight variations in response in the different subjects, within the range of experimental error, might make relatively great differences in the percentage repayment.

SUMMARY AND CONCLUSIONS

The effect of arterial occlusion upon the subsequent rate of blood flow was studied in the hand, forearm, and leg in a series of forty-three normal subjects by means of the plethysmographic method.

Evidence is presented to show that estimation of the blood flow repayment after a minute of arterial occlusion is of much greater value than obtaining a figure which represents the single maximum response to arterial occlusion ("per cent of blood flow debt repaid").

It has been found that grossly there is a direct relationship between the duration of the circulatory arrest and the number of cubic centimeters of excess blood flow over and above the control blood flow level.

The direct application of heat has a more potent vasodilating effect upon skin vessels in the hand than the stimulus elicited by a period of arterial occlusion.

The occurrence of a negative phase (reduction of blood flow to less than the control level) in the hand during the period of reactive hyperemia is probably due to the effect of noxious stimuli upon the tonus of the sympathetic nervous system.

These quantitative studies of reactive hyperemia bear out previous observations that the vascular responses of the forearm and leg differ from those in the hand.

If the excess blood flow during reactive hyperemia is considered as a repayment of the blood flow "debt" which is incurred during the period of arterial occlusion, certain conclusions can be drawn concerning the resting blood flow to the various regions which we studied.

Under optimal environmental conditions and at a bath temperature in the range of 14° to 32° C., the blood flow in the forearm and, to a lesser extent, in the leg appears to be regulated chiefly by the metabolic needs of the tissues; at higher bath temperatures, i.e., around 43° C., it exceeds this level. In the hand the resting blood flow is generally greater than that necessary for metabolic requirements, except at extremely low bath temperatures, when the function of heat dissipation is no longer operative.

The authors wish to thank Dr. Sidney M. Fierst and Mrs. Robert Senior for their assistance in carrying out the experiments.

REFERENCES

1. Grant, R. T., and Pearson, R. S. B.: The Blood Circulation in the Human Limb; Observations on the Differences Between the Proximal and Distal Parts and Remarks on the Regulation of Body Temperature, *Clin. Sc.* 3: 119, 1938.
2. Capps, R. B.: A Method of Measuring Tone and Reflex Constriction of the Capillaries, Venules and Veins of the Human Hand with the Results in Normal and Diseased States, *J. Clin. Investigation* 15: 229, 1936.
3. Kunkel, P., Stead, E. A., Jr., and Weiss, S.: Blood Flow and Vasomotor Reactions in the Hand, Forearm, Foot and Calf in Response to Physical and Chemical Stimuli, *J. Clin. Investigation* 18: 225, 1939.
4. Abramson, D. I., and Ferris, E. B., Jr.: Responses of Blood Vessels in Resting Hand and Forearm to Various Stimuli, *AM. HEART J.* 19: 541, 1940.
5. Freeman, N. E., Shaw, J. L., and Snyder, J. C.: The Peripheral Blood Flow in Surgical Shock. The Reduction in Circulation Through the Hand Resulting from Pain, Fear, Cold and Asphyxia with Quantitative Measurements of the Volume Flow of Blood in Clinical Cases of Surgical Shock, *J. Clin. Investigation* 15: 651, 1936.
6. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, *Am. J. Physiol.* 113: 384, 1935.
7. Bier, A.: Die Entstehung des Collateralkreislaufs. I. Der arterielle Collateralkreislauf, *Arch. f. path. Anat.* 147: 256 and 444, 1897.
8. Moskowicz, L.: Die Diagnose des Arterienverschlusses bei Gangraena Pedis, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* 17: 216, 1907.
9. Roy, C. S., and Brown, J. G.: The Blood-pressure and its Variations in the Arterioles, Capillaries and Smaller Veins, *J. Physiol.* 32: 323, 1879.
10. Lewis, T., and Grant, R.: Observations Upon Reactive Hyperemia in Man, *Heart* 12: 73, 1925.
11. Abramson, D. I., Zazeela, H., and Marrus, J.: Plethysmographic Studies of Peripheral Blood Flow in Man. I. Criteria for Obtaining Accurate Plethysmographic Data, *AM. HEART J.* 17: 194, 1939. II. Physiologic Factors Affecting Resting Blood Flow in the Extremities, *AM. HEART J.* 17: 206, 1939. Ferris, E. B., Jr., and Abramson, D. I.: Description of a New Plethysmograph, *AM. HEART J.* 19: 233, 1940.
12. Lefèvre, J.: *Chaleur Animale et Bioénergétique*, Paris, 1911, Masson et Cie, p. 319.
13. Ferris, E. B., Jr., and Abramson, D. I.: Blood Flow in the Extremities Under Normal and Abnormal Conditions, *Am. Assoc. for the Advancement of Sc. Publication No. 13*, 314, 1940.

THE BLOOD PICTURE IN RHEUMATIC FEVER

VALENTINA P. WASSON, M.D., EDWARD E. BROWN, M.D., AND
CLARICE WEINTRAUB, B.A.
NEW YORK, N. Y.

BECAUSE of the absence of a specific diagnostic test for rheumatic fever, we undertook a detailed study of children with acute rheumatic fever. We hoped thereby to shed new light on this malady, which is so obvious in its acute manifestations, so elusive in its subacute state, and so charged with uncertainty when it is quiescent.

In this paper* we shall present several observations on the hematologic picture of 100 hospital patients who were suffering from the disease. Although the blood picture of acutely ill rheumatic patients shows definite, nonspecific changes, they would be of little value in a new, clinically undiagnosed case of rheumatic fever, i.e., one not characterized by pharyngitis or tonsillitis, carditis, fever, or joint or muscle pains. But these nonspecific changes are of value in the prognosis of clinically established, acute rheumatic fever, and of even greater value in estimating the rise and fall of rheumatic activity in a patient who is known to have had the disease. If frequently and accurately repeated, the blood studies on a rheumatic child give a correct index of his status.

Table I summarizes our laboratory work:

TABLE I

NUMBER OF PATIENTS STUDIED, 100; GIRLS, 53; BOYS, 47; AVERAGE AGE, 10½ YEARS

1. Erythrocyte sedimentation rate estimations	1351 during 32 months
2. Nonfilament neutrophil counts	1195 during 32 months
3. Hemoglobin estimations	1164 during 32 months
4. Blood platelet counts	824 during 20 months
5. Coagulation time estimations	721 during 16 months
6. Bleeding time estimations	595 during 15 months
7. Capillary resistance estimations	639 during 22 months
Total	7487

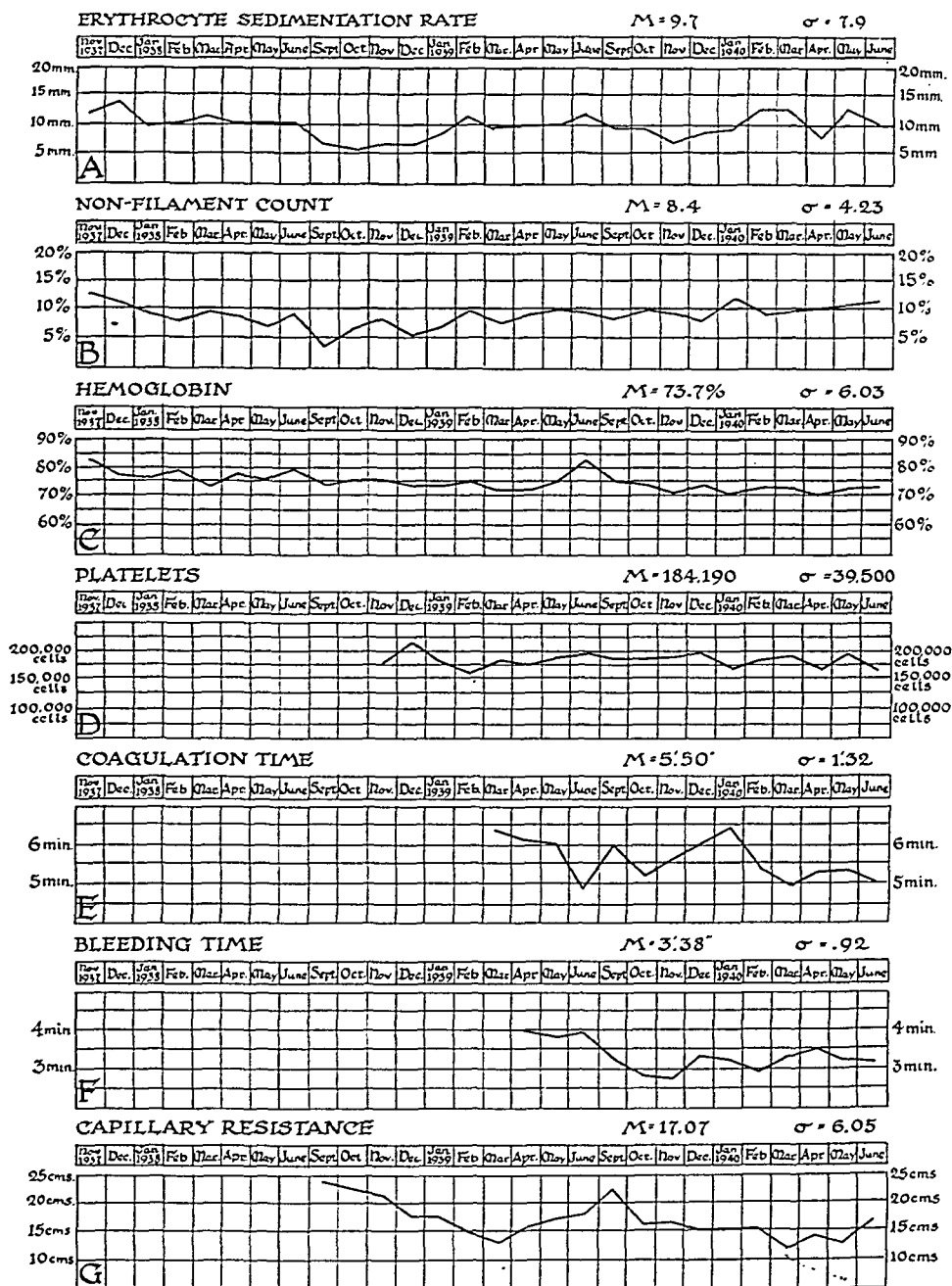
The Erythrocyte Sedimentation Rate is the test most widely used in the diagnosis of rheumatic infection. The following are the observations of some authorities on the significance of this test. Weiss¹ followed the E. S. R. curves in fifty cases of acute rheumatic fever. The rate returned to normal three to seven weeks after the disappearance of complaints. Severity of joint manifestations was not accompanied

Received for publication Dec. 21, 1940.

*Our investigation was carried out at the Pediatric Cardiac Research Clinic of the New York Post-Graduate Hospital & Medical School, on a grant from the John and Mary R. Markle Foundation.

by a proportionately higher E. S. R. Patients with acute rheumatic fever should not be discharged until the sedimentation rate is normal. Payne² found that there was a close relationship between the clinical manifestations and the E. S. R.; the latter was of most practical value in following the progress of the patients. Failure to return to normal indicated that some pathologic process still persisted. Bach and Hill³ observed that the test was of importance as an aid in the initial differentiation between active and nonactive juvenile rheumatism. It was also important if done at regular intervals during convalescence. Hill's⁴ opinion was that, if the E. S. R. was normal, active rheumatism, other than chorea, was not present. Struthers and Bacal⁵ studied thirty-one patients with rheumatic infection who had 573 E. S. R. estimations and 298 leucocyte counts. They observed that the E. S. R. required months to return to normal, and was the most delicate test for activity of the rheumatic infection. In the presence of cardiac failure with edema, it fell rapidly to levels below normal, and was of serious prognostic significance. Landau⁶ discussed the microsedimentation (Linzenmeier-Raunert) method and said that the chief importance of repeated estimations was in indicating the intensity of the acute rheumatic process. The sedimentation rate had to be normal before one could say that the infection had run its course. In uncomplicated chorea the values were low. Elghammer⁷ used the Raunert method on 171 patients who were convalescing from various types of rheumatic infections. He found that the E. S. R. served as an indication of rheumatic activity when there were no symptoms. It was valuable in estimating general progress and prognosis. Persistence of a high E. S. R. signified a grave prognosis. Clifton⁸ came to the following conclusions: Chorea is the only rheumatic manifestation characterized by a normal sedimentation rate. Active rheumatic infection produces a rapid E. S. R. when arthritis or carditis occurs either alone or as a complication of chorea. Monocyclic rheumatic infection subsides in about two months, as indicated by the sedimentation rate. Coburn and Kapp⁹ said that the E. S. R. might be considered a measure of the extent of inflammation. Struthers and Bacal,¹⁰ in their study of 100 cases of rheumatic fever, concluded that the sedimentation rate was the most valuable means of measuring the activity of the rheumatic disease in childhood. Massell and Jones¹¹ studied 178 patients with active rheumatic fever and found that both the corrected E. S. R. and the leucocyte count were valuable aids in following the course of rheumatic infection, but that the E. S. R. was more useful as a single, isolated test, because the leucocyte count was valueless unless done repeatedly. Massell,¹² in a later publication, said that the E. S. R. was a nonspecific reaction, did not differentiate one disease from another, and had no diagnostic value. He stated that its chief usefulness lay in its ability to detect the presence of a disease process in the absence of all other signs. Struthers¹³ contended that

the E. S. R. was probably the most delicate indication of rheumatic activity, and that it was the last abnormality to disappear after activity had ceased.



Graph I.—Mean seasonal distribution of blood findings on 100 rheumatic fever children.

In our studies we used the Linzenmeier-Raunert method of micro-sedimentation described by Landau.⁶ When the same technician did all the tests, we found it simple and accurate for outpatient work. The micromethod has been found equally useful by Elghammer⁷ and Rogatz.¹⁴ The latter used the Smith micrometric apparatus. He states that the micromethod which requires the minimal amount of capillary blood

(obtained by a finger prick) is satisfactory and reliable. In our opinion the Linzenmeier method is accurate only up to 50 mm. per hour of sedimentation, after which it becomes difficult to estimate the rate because of packing of the short tube with erythrocytes. The high normal value is taken as 10 mm. per hour. We have also found that the E. S. R. rises during the premenstrual period, and therefore, unless an inquiry is made concerning the menstrual cycle, and other blood findings are taken into account, a serious mistake may occur.

Graph I *A* represents the distribution of the mean E. S. R. estimations in 100 cases of rheumatic fever, active and inactive, over thirty-two months. It will be observed that the highest peaks in the graph correspond to the seasons of greatest rheumatic fever activity, which are reached in November and March, and that there was a slight fall in January and February, and a marked fall from June to September. The mean E. S. R. for the group was 9.7 mm. per hour.

Among the 100 patients who were studied for thirty-two months, fifty-five attacks of rheumatic fever occurred. Twenty-nine patients had thirty-five of these attacks under our observation, either in the wards or in their homes. Of the remaining twenty attacks, some were reported only after the children had stayed for a prolonged period at home in the care of private physicians, and others were seen at the clinic only at the outset of the illness, whereupon the patients were hospitalized in other institutions. In these twenty instances only the record during quiescence was available.

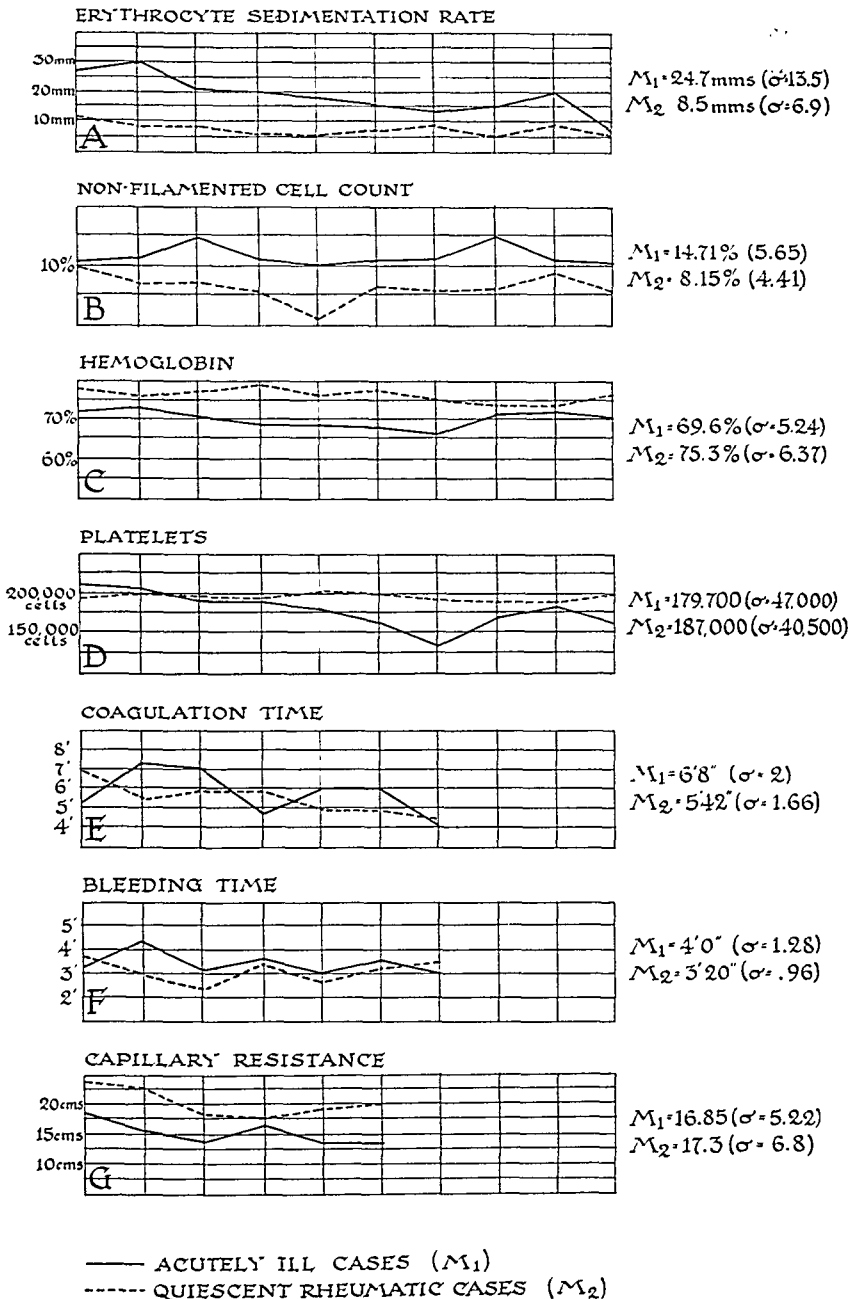
Graph II *A* shows the average trend in the sedimentation rates of the acutely ill and the well rheumatic children. The mean E. S. R. of the acutely ill group was 24.7 mm. per hour, whereas in the well group it was 8.05 mm. per hour. It will be noted that the standard deviation for the first group was abnormally high because of the difficulty of reading values over 50 mm. by the micromethod.

TABLE II

	NO.	MEAN	SIGMA
Total number of patients	100	8.05 mm.	6.9
Boys	47	7.3 mm.	5.7
Girls, all ages	53	8.8 mm.	6.65
Girls menstruating	21	9.9 mm.	6.8
Girls not menstruating	32	7.7 mm.	6.0

To ascertain how much effect menstruation had, we computed separately the E. S. R. of the boys and girls in the quiescent group. The only infections in this group were transient colds which, at times, produced a moderate rise in the E. S. R., and much chronic sinusitis which we found did not accelerate the sedimentation rate. We also calculated the mean sedimentation rate of twenty-one girls who had begun to menstruate and that of thirty-two who had not yet menstruated. The results are presented in Table II.

The above data show that the mean E. S. R. of girls is higher than that of boys, and that that of menstruating girls reaches the upper limit of normal. The E. S. R. of girls who have not yet reached puberty and that of boys is much the same.



Graph II.—Lines representing an average trend in various blood findings in acutely ill and quiescent rheumatic fever patients.

The *Nonfilamented Neutrophile Count* has only recently become an adjunct to the diagnosis of rheumatic infection, and has not attracted the attention it merits.

The leucocyte count is still regarded by many authorities as an important aid in estimating the intensity of rheumatic infection. We

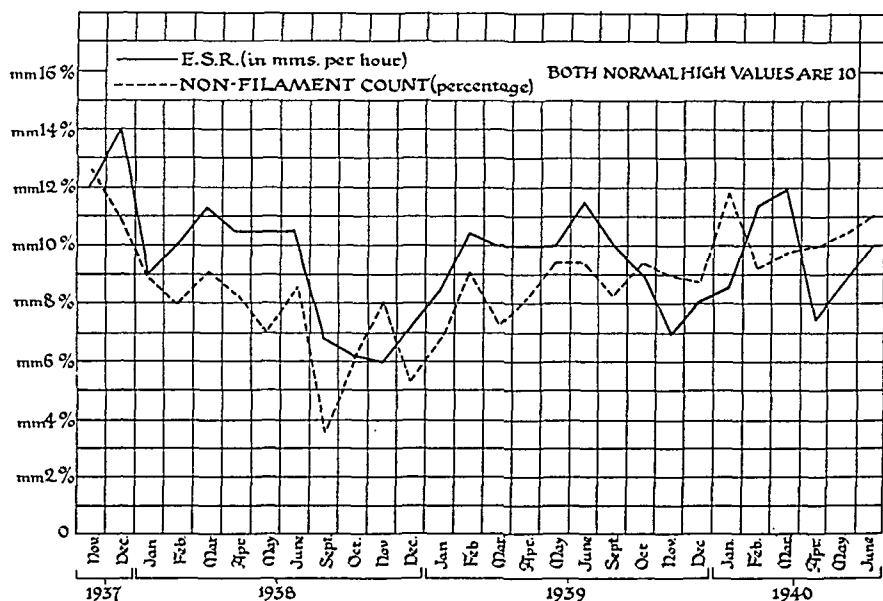
have observed it routinely for four years on all our patients, and have found it unreliable. Even if it is done frequently by the same technician it rarely shows consistent variations, and the personal error is considerable. Therefore, we have abandoned the total leucocyte count in favor of the Schilling count, i.e., the number of nonfilamented neutrophils in the smear. Little has been published on the Schilling count in the diagnosis of rheumatic fever. Clifton⁸ was of the opinion that the Schilling count paralleled the clinical course rather than the subsiding infectious process, and that the E. S. R. was more reliable in the diagnosis of rheumatic activity. Rogatz¹⁵ studied twenty-five cases of rheumatic fever in which both the E. S. R. and the Schilling count were done. He concluded that the E. S. R. was more sensitive as an index of activity and complete convalescence. Both tests were positive when the rheumatic infection was in its early stages, but the Schilling count returned to normal as clinical improvement occurred. Gregg and Allen¹⁶ observed that an increase in the nonfilament count seemed to be more indicative of tissue damage than the polymorphonuclear percentage. Rogatz¹⁷ expressed the view that the Schilling count was of more value than the ordinary differential count in interpreting the clinical manifestations of the acute pathologic conditions of infancy and childhood. King¹⁸ thought that a shift to the left in the number of nonfilamented neutrophils was not so reliable an index of activity as an increased total leucocyte count. Struthers and Bacal,¹⁹ in their study of 100 cases, observed a marked shift to the left in rheumatic fever. In chorea, with a normal sedimentation rate, there was no association between the Schilling count and the E. S. R.

In our group of 100 patients we made 1193 Schilling counts over a period of thirty-two months; the results are given in Graph I *B*. The average percentage of nonfilamented cells was 8.4. It is readily seen that the number of nonfilamented neutrophils parallels the sedimentation rate. The parallelism of the curves is particularly striking when they are superimposed. (See Graph III.)

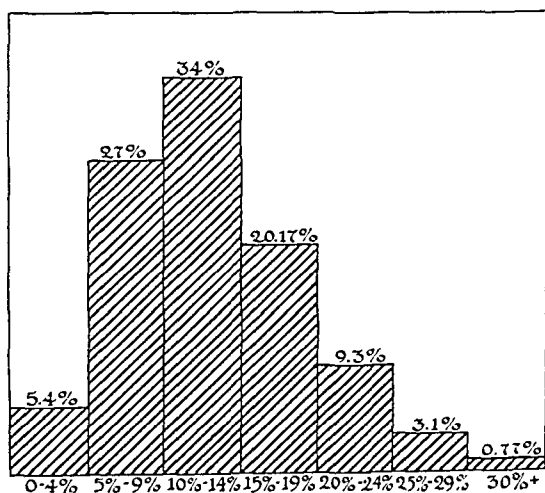
Graph II *B* shows the contrast between the mean nonfilamented cell counts of acutely ill patients and those whose rheumatic infection was quiescent. Again the two curves follow closely the E. S. R. of the ill and well patients, although the nonfilamented neutrophils were slightly slower to rise at the onset of infection, and returned to normal sooner than the E. S. R.

The distribution of the nonfilamented cells among the ill patients is of interest. Graph IV represents the frequency distribution of nonfilamented cells in the thirty-five cases of acute rheumatic fever that occurred among the 100 patients. It will be seen that 54.17 per cent fell into the category of "moderate shift to the left," i.e., between 10 and 20 per cent, and only 13.17 per cent showed a "marked shift to the left."

The opinion prevails that the E. S. R. is a more sensitive index of infection than the nonfilamented cell count, in that it is usually the first evidence of disease. Let us consider our series of acutely ill patients. Of the thirty-five instances of rheumatic fever under our supervision, in eighteen the E. S. R. and the nonfilament count rose simultaneously, in fifteen the E. S. R. rose before the nonfilamented cell count, and in two the reverse occurred. Thus in more than half of the cases the two abnormalities paralleled each other, and in the remaining seventeen cases the rise of the E. S. R. preceded that of the nonfilamented cells in all but two instances.



Graph III.—Mean seasonal distribution of erythrocyte sedimentation rate and non-filament neutrophils in 100 rheumatic fever patients.



Graph IV.—Frequency distribution of nonfilamented neutrophils in acutely ill group.

Let us now consider the terminal stages of an attack of rheumatic fever and see what happens with respect to the return to normal of the E. S. R. and the nonfilamented cell count. Data are available in

only twenty-nine cases, for in six the attacks had not yet run their course. In seven out of twenty-nine the E. S. R. and the cell count returned to normal at the same time, in fifteen the nonfilamented cell count was the first to become normal, and in seven the E. S. R. was first.

If the E. S. R. is to be regarded only as an index of infection, then our small series of cases suggests that the sedimentation rate is the more sensitive of the two tests, both at the beginning and at the end of an attack of acute rheumatic fever, especially the latter. But we must bear in mind that the E. S. R. rises also before menstruation, which may coincide with the beginning or at the end of a rheumatic attack.

The Hemoglobin content of the blood in rheumatic fever gets scant attention in medical writings. Weiss¹ said that anemia always accompanies rheumatic fever. Geselius¹⁹ observed an association between the degree of anemia and the severity of the rheumatic infection. Hubbard and McKee,²⁰ in a study of seventeen cases, spoke of a frequently severe anemia with the active phase of rheumatic fever, and commented that its persistence might often be an indication of continued rheumatic activity. Isaacs, Sturgis, Bethell, and Goldhammer²¹ believed that the occurrence and severity of anemia were an accurate index of rheumatic activity. They also pointed out that the E. S. R. paralleled the severity of the anemia, and that both should be watched in following the course of the disease.

Over a period of thirty-two months we made 1164 estimations of hemoglobin in our group of 100 rheumatic patients. Using the Sahli method, the hemoglobin was measured in grams, from which the percentage was computed (16.7 grams equal 100 per cent).

Graph I C shows the seasonal distribution of the mean hemoglobin curve for the entire group of patients, including those with active and inactive disease. There was a general downward trend from a high peak in November, 1937, toward May, 1938. Then there was an abrupt rise in June to 78.3 per cent. In September the hemoglobin fell to 74 per cent, then maintained a fairly steady level between 75 per cent and 74 per cent until the middle of March, 1939. At that time a fall to 72 per cent occurred, and was maintained until the end of April, when a rapid rise took place, so that by the end of June an average of 82 per cent was attained. In September, 1939, the hemoglobin returned to 75 per cent. During the winter of 1939-40, the hemoglobin was uniformly low, fluctuating between 73.5 per cent and 70 per cent, without the expected rise in May.

In the hope of shedding light on the continuous decline in the mean hemoglobin level of the entire group during three consecutive winters, we present the mean hemoglobin percentage, together with the number of attacks of acute rheumatic fever which were observed during each of the three periods, and the atmospheric temperature for the first six

months of each year, i.e., from January to June, which covers the period of greatest rheumatic activity (Table III).

The steady fall in hemoglobin during the three consecutive winters may have been related to the increasing frequency of rheumatic fever attacks, which, in turn, may have been associated with the steadily diminishing temperature during the three January-to-June semesters. Vital statistics for New York show that the first half of 1938 set a record for low mortality from rheumatic heart disease, and from scarlet fever and pneumonia, as well. It was also the warmest half year of the three, with a temperature of 449° above average. The temperature during the first six months of 1939 was lower. All of the eight attacks of rheumatic fever in our series occurred during that period, and the average hemoglobin dropped 2.3 per cent. The year 1940 was characterized by the coldest and rainiest winter and spring of the three years (precipitation 24.66"), and twelve rheumatic fever attacks out of a total of sixteen occurred between January and June of that year. The hemoglobin was lowest during that winter, and there was no rise in May.

TABLE III

	1937-38	1938-39	1939-40
Mean hemoglobin	77%	74.7%	72.35%
No. of attacks of acute rheumatic fever	11	8	16
No. of attacks between January and June	6	8	12
Mean temperature* from January to June	+449°	+374°	-366°

*These figures represent the cumulative deviation from the mean temperature, as reported by the U. S. Weather Bureau of the first six months of each of the three years.

Graph II C shows the different mean hemoglobin levels of the acutely ill patients and those whose disease was quiescent. In the former it was 69.6 per cent, and, in the latter, 75.35 per cent. Hemoglobin values under 59 per cent occurred in only nineteen of 1164 estimations (1.6 per cent).

Obviously, many factors other than infection and atmospheric temperature determine the hemoglobin content, e.g., diet, hygiene, and hereditary and individual make-up. The latter is important, and that is why one cannot put too much reliance on occasional estimations of hemoglobin in the diagnosis of rheumatic fever. We have normal standards for the sedimentation rate and the nonfilamented cell count, but there are, apart from the acute anemias, only individual standards for hemoglobin. A child who shows no evidence of infection and maintains a steady hemoglobin level of 68 per cent is better off than the one whose hemoglobin suddenly drops from 90 per cent to 75 per cent after an attack of acute tonsillitis.

Platelets, Coagulation and Bleeding Time.—During the first year of our study our observations were confined to the estimation of the

erythrocyte sedimentation rate, nonfilament count, and hemoglobin. In the course of our clinical observations we were much impressed by the frequency of hemorrhagic phenomena in rheumatic patients. Forty-three per cent reported more than two nosebleeds, more than two petechiae at a time were observed in nineteen cases, and 11 per cent of the patients had purpuric spots as a result of insignificant trauma. Hoping to shed more light on the nature of these hemorrhagic symptoms, in the fall of 1938 we added a routine platelet count to our study, and, a few months later, when our laboratory facilities expanded, the estimation of coagulation and bleeding time.

This study particularly interested us because there is almost no mention of it in medical writings, although a great deal has been written about the blood-clotting mechanism and the purpuras, and some attention has been given to hemorrhagic manifestations in scarlet fever. We present here the few references that have a direct bearing on this study and on our observations. The most valuable monograph on blood platelets is that of Tocantins.²² He observed that during the acute stage of infectious diseases, including rheumatic fever, there is a thrombopenia which gives place at the termination of the infection to moderate thrombocytosis. The thrombopenia and the decrease in the number of platelets correspond to the duration of fever. Tocantins is the only writer who refers directly to rheumatic fever. Hunt²³ said that hemorrhages come on usually after the subsidence of the acute symptoms of scarlet fever, and seem to be caused by the action of scarlatinal toxin on the endothelium of the blood vessels. In most cases there were a sharp reduction in the platelets and prolongation of the bleeding time. Coburn²⁴ said that the frequency of epistaxis, purpura, hematuria, and hemorrhagic pulmonary consolidation during the activity of the rheumatic process strongly suggested that there were physiologic changes causing increased permeability of the capillaries and small blood vessels. Sturgis, Isaacs, Goldhammer, and Bethell,²⁵ in their review of publications on the hemorrhagic state, noted that bleeding may result from the decrease in blood platelets, alteration in the plasma, or changes in the permeability of the capillaries. Madison and Squier²⁶ found that increased permeability of the capillary walls to erythrocytes is always a pathologic condition and demands an etiologic investigation. They added that capillary erythropermeability is associated with vitamin C deficiency, severe infections, terminal phases of malignant disease, malignant hypertension, primary blood disease, allergic states, and ovarian disorders. McKhann and Edsall²⁷ were of the opinion that purpura implies some factor which causes a reduction in blood platelets. The presence of purpuric manifestations in allergic states, as well as in infections, suggested to them an imbalance among the various factors which are involved in the normal coagulation process. Elliott²⁸ said that in primary or idiopathic thrombocytopenic purpura the plate-

lets are markedly reduced, or may even be absent, bleeding time is prolonged, and clotting time delayed. He also stated that, in almost all cases, purpura is a symptom complex rather than a disease entity. Rosenthal²⁹ observed that thrombopenic purpura shows uniformity in its blood picture, but presents a marked variation in its course from acute to chronic. He noted a marked diminution in blood platelets, prolongation of the bleeding time, and clot retraction. Fox and Enzer,³⁰ in a paper on the phenomena of purpura following scarlet fever, expressed the opinion that the reasonable explanation for the purpura was that scarlet fever toxin strongly affects the capillary epithelium.

Before we present our observations on the subject, we shall review what different authorities regard as normal values for the platelet count and coagulation and bleeding time.

Platelets.—Levinson and McFate:³¹ normal values are from 250,000 to 350,000 per c. mm. of blood. Tocantins:²² average platelet count on normal persons is $250,000 \pm 7,000$ per c. mm. of blood, with a standard deviation of 58,000. Todd and Sanford:³² the normal number of blood platelets, when counted by the direct method, ranges from 200,000 to 300,000 for each c. mm. of blood.

Coagulation Time.—Levinson and McFate:³¹ capillary method, normal time is from three to eight minutes. Pepper and Farley:³³ capillary method, two to four minutes. Nicholson:³⁴ capillary method, two to eight minutes.

Bleeding Time.—Levinson and McFate:³¹ by the Duke method, the normal bleeding time is from three to seven minutes. Todd and Sanford:³² the normal bleeding time is from one to three minutes, but may be as long as eight minutes. Pepper and Farley:³³ in normal persons a small, sharp cut through the skin bleeds from three to six minutes. The bleeding time is in inverse proportion to the number of platelets. Nicholson:³⁴ normal bleeding time is from three to five minutes.

In our study we considered that the normal platelet count is between 250,000 and 350,000 per c. mm., that the coagulation time varies from three to five minutes, with a high normal limit of seven minutes, and that the bleeding time ranges from one to three minutes, with an upper limit of five minutes.

The personal error in our series of computations on platelet counts was $\pm 4,500$ cells. The platelets were counted by the direct citrate method; the coagulation time was ascertained by Zabrazes' capillary method, and the bleeding time by the direct capillary method.

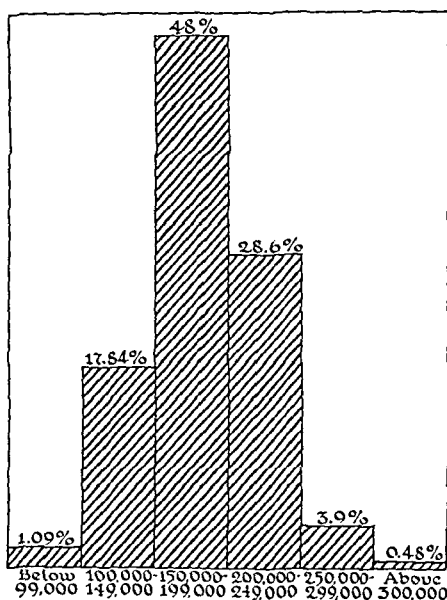
In the course of twenty months we did 824 platelet counts on 100 rheumatic fever patients, and found that only 4.38 per cent had counts above 250,000 cells per c. mm. Graph V shows the frequency distribution of these 824 platelet counts. Nearly one-half were between 150,000 and 200,000, and 66.93 per cent were below 200,000, which is low by all standards. Graph I *D* shows the mean seasonal distribution of platelets through the twenty months of observation. The lowest values occurred in April and May of both years, when the E. S. R. and nonfilamented cell counts were high. The mean platelet count for the whole group was 184,000 per c. mm. There was no appreciable dif-

ference between the counts on boys and girls, nor between menstruating and nonmenstruating girls. The latter observation corroborates Lee and Erickson's³⁵ work on hemophilia and the blood of menstruating women, in that in both conditions there is no reduction of platelets, but a delay in their disintegration. Table IV summarizes the above data.

The platelet count of the acutely ill children was, on an average, 7,300 cells lower than that of the ones whose disease was quiescent. Graph II *D* shows that after the onset of infection there is at first a moderate decrease in blood platelets, followed by a more rapid diminution, and then a rapid recovery at the end of the attack.

TABLE IV

	NUMBER	MEAN	SIGMA
Total patients	100	184,190 platelets	39,500
Boys	47	183,950 platelets	44,740
Girls	53	185,500 platelets	36,000
Girls menstruating	21	185,000 platelets	27,000
Girls nonmenstruating	32	186,900 platelets	27,500



Graph V.—Frequency distribution of platelets in 100 rheumatic children.

Seven hundred twenty-one coagulation time estimations were done on our 100 patients in the course of sixteen months. Graph I *E* shows the mean seasonal variations of the coagulation time. The values were low in May, 1938, and in March and June, 1939, and elevated during the winter months. The mean coagulation time for the group was 5'50". This is well within normal limits, although higher than the average for normal persons. Sex played no role in the length of the coagulation time; that of boys was only a fraction higher than that of girls. There was also no difference between menstruating and nonmenstruating girls. Graph II *E* shows that in the group of children who were suffering

from acute rheumatic fever the mean coagulation time was 6'8", and in the well group it was 5'42".

Five hundred ninety-five bleeding time estimations were recorded in the course of fifteen months on the 100 children. We found that the mean bleeding time for the entire group was 3'38", which is also within normal limits. The average bleeding time for the girls was 3'29", and for the boys eighteen seconds longer. Graph I *F* shows the seasonal variations in the bleeding time of our patients. The longest were recorded in April and June, 1939, and in April, 1940. Graph II *F* shows that the mean bleeding time was four minutes for the acutely ill patients and 3'20" for the well group. Our observations on the coagulation and bleeding times are summarized in Table V.

TABLE V

	COAG. TIME, MEAN	SIGMA	BLEEDING TIME, MEAN	SIGMA
Total Group	5'50"	1.3	3'38"	0.92
Boys	5'56"	1.67	3'47"	1.1
Girls	5'49"	1.5	3'29"	1.03

From the above data it appears that the platelet count is of value in cases of rheumatic fever, because of the uniformly low counts, and because a marked decrease occurs during the later phase of infection, but, as far as the bleeding and coagulation times are concerned, the slight variations are so well within normal limits that as isolated tests they appear to be of no value.

Capillary Resistance.—We also sought an explanation for rheumatic hemorrhagic phenomena in capillary permeability. A detailed article by us³⁶ on the subject of capillary resistance in rheumatic fever is being published elsewhere. Therefore, we shall present data which are pertinent only to this report.

Capillary erythropermeability has been attracting considerable attention lately. We have already mentioned the article of Madison and Squier²⁶ on the subject. Wilder and Wilbur³⁷ observed that increased capillary fragility is nonspecific, and occurs in a variety of conditions other than vitamin C deficiency. They also showed that patients with scurvy fail to give evidence of increased capillary fragility. Greene,³⁸ in his discussion of the variation in capillary resistance of the same children at different times, concluded that a positive reaction to the capillary resistance test does not necessarily denote an insufficient intake of vitamin C. Zander,³⁹ in his article on inflammatory changes in blood vessels, said that bacterial agents, after an increased initial resistance, produce a diminished resistance to capillary permeability. When inflammation is present in a sensitized animal the preliminary period is shortened and the capillary fragility hastened. Rossman⁴⁰ observed that artificially induced fever causes an immediate decrease in capillary resistance. Brown⁴¹ noted increased capillary permeability in scarlet fever.

Out of our group of 100 patients, only eighty had capillary resistance studies sufficiently extensive to be included in this article. We used exclusively the simple method described by Dalldorf.⁴² We found that the Dalldorf capillary resistometer was an effective means of estimating accurately and repeatedly the capillary erythropermeability. Abt, Farmer, and Epstein⁴³ reported that the normal capillary resistance of 10-year-old children was 23 cm. of negative pressure. The average age of the patients in our group was 10.5 years. Our average for the group of rheumatic fever patients over a period of twenty-two months of study was 17.07 cm. of negative pressure. The highest mean capillary resistances were recorded in September, 1939 (24 cm.), and in September, 1940 (23 cm.); the lowest were noted in March, 1939 and 1940, when they were 13 and 12 cm., respectively (See Graph I *G*). The latter coincided with the onset of rheumatic activity and remained at a low level until May of both years, when clinical and hematologic improvement occurred.

Forty-six estimations of erythropermeability were made during fourteen attacks of acute rheumatic fever. The mean capillary resistance of ill children was 16.85 cm., and that of well patients averaged 17.3 cm. (See Graph II *G*). The capillary resistance of the boys was 17.3 cm., and, of the girls, 16.7 cm. The greatest capillary permeability was noted in forty-three children who had had repeated nosebleeds. Their capillary resistance was only 16.6 cm., whereas that of those who had had no bleeding was 18.6 cm.

These data are presented in Table VI.

TABLE VI

TOTAL NUMBER OF PATIENTS, 80	BOYS, 39	GIRLS, 41
Average for the Group	17.07 cm.	Sigma 6.05
Average for the Boys	17.30 cm.	Sigma 6.60
Average for the Girls	16.70 cm.	Sigma 6.00
Average for the Bleeders	16.60 cm.	Sigma 5.05
Average for the Nonbleeders	18.60 cm.	Sigma 7.75

COMMENT

Our study corroborates the prevailing opinion that the erythrocyte sedimentation rate is the most delicate nonspecific indication of rheumatic infection. In using it, allowance must be made for the premenstrual period, and also for acute anemias, which we did not encounter in our group of patients. The mean E. S. R. of menstruating girls is higher than that of girls under puberty and of boys.

The E. S. R. is valuable as an isolated test because of its sensitivity to the presence of infection and because of its well-established normal values. In thirty-three of our thirty-five cases of acute rheumatic fever the E. S. R. was abnormal at the outset of the attack; in one case it rose late; and in only one did it never rise, even in the presence of

other hematologic and clinical evidences of infection. Many transient upper respiratory infections in our cases were accompanied by a moderate rise in the E. S. R. but it would fall to normal within a few days. When an upper respiratory infection ushered in an attack of rheumatic fever, the E. S. R. would remain accelerated or would continue to rise after the symptoms of the cold had subsided. A single E. S. R. estimation when the patient is not menstruating indicates merely the presence or absence of an infection, and, even when the child is known to be rheumatic, does not necessarily indicate an exacerbation of the disease, but often just the presence of an intercurrent infection. Only the trend of the E. S. R. curve, together with other clinical and laboratory aids, has diagnostic importance. In cases of acute rheumatic fever, the E. S. R. takes, on an average, two months to return to normal. When the E. S. R. returns to normal in the course of a few days, or even two weeks, it means that the patient has had an infection other than rheumatic fever.

The nonfilamented neutrophile count is an important diagnostic criterion of infection. It is not so sensitive as the E. S. R., but has the advantage that an increase in the nonfilamented cells is always evidence of infection, and often a severe one. With most transitory colds, the Schilling count in our cases remained normal, whereas the E. S. R. was moderately accelerated. We found that a cold which was unaccompanied by an increase in the nonfilamented cells gave us less cause for concern than one accompanied by a count above 10 per cent. During acute attacks of rheumatic fever the nonfilamented cell count closely paralleled the trend of the sedimentation rate, except in the terminal stages, when it returned to normal sooner than the E. S. R. A normal Schilling count does not mean that infection is absent, but it does mean that either the infection is trivial or is just beginning, and that there is, as yet, no effect on the bone marrow.

The hemoglobin level is an unreliable standard of activity, if used as an isolated test. Only the trend of the hemoglobin curve has significance in a given case. In evaluating the intensity of infection with the aid of hemoglobin estimations, the question should always be asked: what is the patient's average hemoglobin level during periods of rheumatic inactivity? The average, not the maximum, should be taken for comparison, because even in health the hemoglobin exhibits marked variations. Very few of the children in our series had a hemoglobin under 59 per cent, but many showed a sudden and significant fall, amounting to 15 per cent, during an acute infection. Hence a single estimation is useless, and only repeated estimations which indicate a downward trend in hemoglobin may be considered significant.

In our effort to account for the hemorrhagic phenomena of rheumatic fever, our attention was first turned to the blood platelets. Of 823 counts on the entire group of patients, 66.93 per cent were below 200,000,

and only 4.38 per cent were above 250,000. We wish to draw special attention to this sharply subnormal platelet count in children who are subject to rheumatic fever; it characterizes the quiescent state as well as the acute. There was no difference between the boys and the girls in this respect. The presence of an acute infection produced a sharp decrease in the platelets only toward the end of the attack, and this was followed by a rapid rise.

The estimation of bleeding and coagulation time shed little light on the bleeding tendency of rheumatic fever patients. Both showed marked seasonal variations which were coincident with peaks of infection, but these variations were so obviously normal that for diagnostic purposes they had no significance. As in the case of hemoglobin, knowledge of the average bleeding and coagulation times for each patient during the quiescent period is of importance in appreciating the variations during disease.

We found that the estimation of capillary resistance was important in the diagnosis of the rheumatic state. The test is easy to perform, normal values are known, and both patients with active and inactive rheumatic disease show considerable deviations from the normal. The lowest capillary resistances were observed in children who had had repeated attacks of epistaxis. The capillary resistance displayed marked seasonal variations; the lowest erythropermeability occurred during the spring months, when the incidence of rheumatic fever attacks was greatest.

It appears that the hemorrhagic tendency of the rheumatic state may be explained by (1) the generally low blood platelet level, with further reduction during the acute phase of the disease, and (2) the increased capillary erythropermeability of all rheumatic fever patients, especially those who are prone to nosebleeds and have acute attacks of fever.

CONCLUSIONS

Seven tests are enumerated below in the order of their diagnostic significance.

1. The erythrocyte sedimentation rate is the most delicate means of detecting the presence of an infection, even a trivial one. In the absence of clinical manifestations, it is an error to assume that rheumatic infection is present when an elevation of the sedimentation rate is the only abnormality. The E. S. R. is accelerated when there is anemia and before menstruation. It is important as a routine test in cases of known rheumatic disease, and is even more valuable in following the course of an acute attack.

2. The nonfilamented neutrophile count is not so delicate a test as the sedimentation rate, but should be used routinely on all patients with rheumatic fever, because an increase in the number of nonfilamented neutrophiles *always* indicates the presence of an infection, often a severe one. As an isolated test it is important.

3. The capillary resistance is next in diagnostic importance, not only because of the generally increased erythropermeability of rheumatic fever patients, but also because of the marked variations in the active and inactive phases of the disease. It is lowest in children who are prone to hemorrhagic phenomena.

4. Sixty-six and ninety-three hundredths per cent of the platelet counts on our patients were below 200,000 per c. mm. There is a progressive reduction of platelets during the initial phases of an acute attack, with a marked fall during the later weeks, followed by a rapid rise.

5. The hemoglobin estimation is not important as an isolated test unless the trend of the hemoglobin curve of the patient is known.

6. and 7. Coagulation and bleeding time estimations offer no aid in the diagnosis of rheumatic fever because their variations are practically always within normal limits, although in acutely ill patients they tend to show high normal values.

REFERENCES

1. Weiss, A.: A Prognostic Value of the Sedimentation Rate in Arthritis—A Modification of the Technique, *Am. J. M. Sc.* 181: 379, 1931.
2. Payne, W. W.: Acute Rheumatism and the Sedimentation Rate, *Lancet* 1: 74, 1932.
3. Bach, F., and Hill, N. G.: Erythrocyte Sedimentation Rate in Rheumatic Fever, *Lancet* 1: 75, 1932.
4. Hill, N. G.: The Erythrocyte Sedimentation Rate in Juvenile Rheumatism, *British J. Child. Dis.* 29: 181, 1932.
5. Struthers, R. R., and Bacal, H. L.: Determination of the Activity of Rheumatic Infection in Childhood, *Canad. M. A. J.* 29: 470, 1933.
6. Landau, A.: Microsedimentation (Linzenmeier-Raunert Method), *Am. J. Dis. Child.* 45: 691, 1933.
7. Elghammer, H. W.: Erythrocyte Sedimentation Rate in Rheumatic Infection, *Arch. Pediat.* 51: 281, 1934.
8. Clifton, W. M.: Rate of Sedimentation of the Erythrocytes in Rheumatic Infection in Children, *Am. J. Dis. Child.* 52: 1093, 1936.
9. Coburn, A. F., and Kapp, E. M.: Observations on the Development of the High Blood Sedimentation Rate in Rheumatic Carditis, *J. Clin. Investigation* 15: 715, 1936.
10. Struthers, R. R., and Bacal, H. L.: Rheumatic Infection in Childhood: Observations on the Sedimentation Rate and the Schilling Count, *Canad. M. A. J.* 35: 258, 1936.
11. Massell, B. F., and Jones, T. D.: Evaluation of the Signs of Active Rheumatic Fever with Special Reference to the Erythrocyte Sedimentation Rate and the Leukocyte Count, *New England J. Med.* 215: 1269, 1936.
12. Massell, B. F.: Clinical Application of the Sedimentation Rate, *J. Pediat.* 12: 681, 1938.
13. Struthers, R. R.: Rheumatic Heart Disease in Adolescence, *Canad. M. A. J.* 42: 128, 1940.
14. Rogatz, J. L.: Microsedimentation of the Erythrocytes in Infants and in Children, *Am. J. Dis. Child.* 56: 1037, 1938.
15. Rogatz, J. L.: The Comparative Value of the Schilling Differential Blood Count and the Sedimentation Rate of the Erythrocytes in Acute Rheumatic Fever in Childhood, *J. Pediat.* 8: 184, 1936.
16. Gregg, R. O., and Allen, E. G.: Erythrocyte Sedimentation Test Observations on Sedimentation Rate and Leukocyte Changes in 103 Hospital Cases, *New York State J. Med.* 39: 2192, 1939.
17. Rogatz, J. L.: Schilling Blood Count in the Prognosis of Acute Infections in Infancy and in Childhood, *Am. J. Dis. Child.* 40: 70, 1930.

18. King, R. L.: Symptoms and Signs of Rheumatic Fever, *J. Pediat.* 14: 404, 1939.
19. Gezelius, G.: Anemia with Rheumatic Fever, *Am. J. Dis. Child.* 59: 642, 1940.
20. Hubbard, J. P., and McKee, M. H.: The Anemia of Rheumatic Fever, *J. Pediat.* 14: 67, 1939.
21. Isaacs, R., Sturgis, C. C., Bethell, F. H., and Goldhamer, S. M.: Blood: Review of Recent Literature, *Arch. Int. Med.* 65: 1211, 1940.
22. Tocantins, L. M.: The Mammalian Blood Platelet in Health and Disease, *Medicine* 17: 155, 1938.
23. Hunt, L. W.: Hemorrhagic Purpura in Scarlet Fever: Report of 2 Cases, *Am. J. Dis. Child.* 56: 1086, 1938.
24. Coburn, A. F.: Factors of Infection in the Rheumatic State, Williams and Wilkins, 1931.
25. Sturgis, C. C., Isaacs, R., Goldhamer, S. M., and Bethell, F. H.: Blood: Review of the Literature, Conclusion, *Arch. Int. Med.* 64: 148, 1939.
26. Madison, F. W., and Squier, T. L.: Bleeding Due to Capillary Defect, *Wisconsin Med. J.* 39: 31, 1940.
27. McKhann, C. F., and Edsall, G.: Characteristics of Blood Clot Formation, Significance in Pediatric Practice, *Pennsylvania Med. J.* 42: 731, 1939.
28. Elliott, R. H. E.: Diagnostic and Therapeutic Considerations in the Management of Idiopathic Thrombocytopenic Purpura, *Bull. New York Acad. Med.* 15: 197, 1939.
29. Rosenthal, N.: The Course and Treatment of Thrombopenic Purpura, *J. A. M. A.* 112: 101, 1939.
30. Fox, M. J., and Enzer, N.: A Consideration of the Phenomenon of Purpura Following Scarlet Fever, *Am. J. M. Sc.* 196: 321, 1938.
31. Levinson, S. A., and MacFate, R. P.: Clinical Laboratory Diagnosis, Lea and Febiger, 1937, page 377.
32. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis and Laboratory Methods, W. B. Saunders Co., 1939, Ed. 9, page 244.
33. Pepper, O. H. P., and Farley, D. L.: Practical Hematological Diagnosis, W. B. Saunders Co., 1933, page 173.
34. Nicholson, D.: Laboratory Medicine, Lea and Febiger, 1934, page 160.
35. Lee, P., and Erickson, B. N.: Platelet Studies in Menstruation and Hemophilia: Total and Differential Counts, Disintegration Rates and Lipid Determination, *Proc. Soc. Exper. Biol. & Med.* 39: 264, 1938.
36. Brown, E. E., and Wasson, V. P.: Capillary Resistance in Rheumatic Children, *J. Pediat.* (118: 3, 1941).
37. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch. Int. Med.* 59: 512, 1937.
38. Greene, D.: Evaluation of the Capillary Resistance Test in the Diagnosis of Subclinical Scurvy, *J. A. M. A.* 103: 4, 1934.
39. Zander, E.: Changes in Blood Vessels (Capillary Fragility) with Inflammation, *J. Exper. Med.* 66: 637, 1937.
40. Rossman, P. L.: Capillary Resistance in Artificially Induced Fever, *Ann. Int. Med.* 14: 281, 1940.
41. Brown, E. E.: Capillary Resistance in Scarlet Fever, *Arch. Pediatrics* 57: 553, 1940.
42. Dalldorf, G.: A Sensitive Test for Subclinical Scurvy in Man, *Am. J. Dis. Child.* 46: 794, 1933.
43. Abt, A. F., Farmer, C. I., and Epstein, I. M.: Normal Cevitamic (Ascorbic) Acid Determinations in Blood Plasma and Their Relationship to Capillary Resistance, *J. Pediat.* 8: 1, 1936.

VENOUS PRESSURE RESPONSES TO EXERCISE

PRELIMINARY REPORT

P. SZEKELY, M.D.

LONDON, ENGLAND

THE main reason why measurement of the venous blood pressure is not adapted to routine clinical use is that the results obtained by the usual technique are not sufficiently reliable to be of great clinical importance. Venous pressure readings on normal persons, as recorded by different authors, show a wide variation. The range of this variation is still greater when different methods are compared. In many cases of heart disease with decreased functional capacity of the cardiovascular system, the venous pressure at rest is within normal limits, and it rises only when there is clinical evidence of congestive heart failure. Certain American authors¹ stated recently that, in their experience, venous pressure measurements have been of little diagnostic aid in borderline cases of congestive heart failure.

For this reason, efforts have been made to devise a method of measuring the venous pressure during and after bodily exercise, in order to obtain a more reliable evaluation of the pathophysiologic events in the cardiovenous system.

Venous pressure responses to exercise have been investigated by Hooker,² Schott,³ Villaret, and others,^{4, 5} Bedford and Wright,⁶ White, Barker, and Allen,⁷ Schneider and Collins,⁸ and, recently, by Nieuwenhuizen.⁹ All these authors observed a rise of venous pressure with muscular exertion which lasted usually throughout the whole period of the activity. White, Barker, and Allen⁷ found in normal subjects that the venous pressure rose a few centimeters of water during exercise. It fell to, or below, the control level immediately on cessation of the exercise. Subjects with congestive heart failure had a high resting venous pressure, which rose considerably on exercise and did not return to normal when it ceased. Nieuwenhuizen⁹ followed the venous pressure for ten minutes after exercise, and arrived at the conclusion that in normal subjects the venous pressure falls to its resting level within fifteen seconds after exercise. He observed in cases of slight congestive heart failure that the resting value was normal, and that only the response to exercise betrayed the pathologic condition.

This preliminary report is based upon 122 exercise tests on eighty patients. The group is small, and the purpose of this article is not to

From the Cardiac Clinic of the Medical Faculty of Paris.
Received for publication Jan. 4, 1941.

draw conclusions, but to record our observations. We believe that the results we obtained may be of interest and value for further investigations.

METHOD

We employed the air-filled system, with an aneroid manometer. This method is suitable for clinical use, and even for serial measurements lasting some minutes, when technical precautions are strictly maintained. For details of the technique, reference should be made to the works of Villaret, and others,¹⁰ and Bedford and Wright.⁶ After having ascertained the resting value, the subject was told to raise, successively, the right and left leg ten times each, keeping the upper part of the body as still as possible. The venous pressure was taken immediately on cessation of the exercise, and then thirty seconds, and one, two, and three minutes after it ceased. In this way a venous pressure curve consisting of six readings was obtained. In some cases, the communication between manometer and vein was maintained during the whole experiment, even during exercise, and the readings so taken were compared with those obtained on the same subjects when communication had been interrupted, and restored only at the moment of the measurements. No differences were found. The needle, the metal nozzle, and the short piece of rubber tubing were syringed with 3.8 per cent sodium citrate solution just before the experiment, in order to avoid blood coagulation. The blood usually remained fluid until the end of the experiment (four to five minutes); if it did not, which happened very rarely, the results were rejected.

RESULTS

In eight cases, in which there was neither clinical nor electrocardiographic evidence of heart disease, the resting venous pressure was normal (from 6 to 12 cm. of water). It rose about 2 to 5 cm. of water during exercise, and returned to the basal level within thirty seconds after exercise was stopped (see Fig. 1). These observations are in agreement with those of White, Barker, and Allen,⁷ and Nieuwenhuizen.⁹

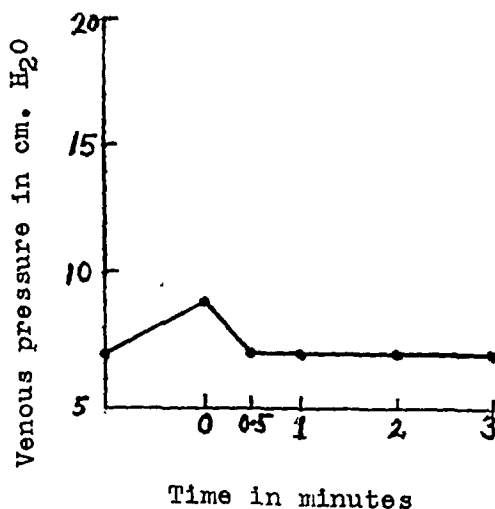


Fig. 1.—Normal venous pressure response to exercise.

In thirty-eight out of fifty-four cases (70.3 per cent) in which there was clinical evidence of congestive heart failure, the resting venous

pressure was increased (above 12 cm. of water), and the response to exercise was a pathologic one, irrespective of the nature of the cardiac disease. The venous pressure showed a greater rise during exercise, and it either returned to the initial level more slowly than in normal subjects, or not at all during the period of observation. In twelve of the sixteen cases of this group in which the resting values were normal, the venous pressure curve after exercise was pathologic in the sense mentioned above, which was in keeping with the clinical evidence of venous engorgement. In four cases, both the resting value and that after exercise were within normal limits.

Of eighteen patients with heart disease without any clinical evidence of congestive heart failure and with a normal venous pressure at rest, eight exhibited a normal response to exercise. In the remaining ten cases, the venous pressure rose considerably during exercise and fell below the initial level after it. This fall of the venous pressure after exercise has been noted by Nieuwenhuizen,⁹ who explained it as a regulative mechanism. He stated that this kind of response may indicate latent congestive heart failure.

In our experience, auricular fibrillation, *per se*, does not alter the venous pressure. In our cases of auricular fibrillation, the venous pressure was increased only when the fibrillation was associated with congestive heart failure. However, in cases of auricular flutter the venous pressure seemed to be rather subject to pathologic alterations. It is difficult to explain this observation. The question whether the mechanism of auricular flutter, *per se*, is able to alter one or more factors which are responsible for the maintenance of normal peripheral venous pressure requires further investigation.

ILLUSTRATIVE CASES

CASE 1.—L. P. was a man, aged 60, who had heart sounds of poor quality and a presystolic gallop rhythm. His blood pressure was 190/100. There was no evidence of venous engorgement. Roentgenologically, the left ventricle was enlarged. The electrocardiogram showed complete A-V heart block. The blood Wassermann reaction was negative. The venous pressure was normal at rest, and fell below the initial level after exercise (Fig. 2). Diagnoses: complete heart block, probably caused by coronary sclerosis; no clinical signs of congestive heart failure; venous pressure normal at rest, with a pathologic response to exercise which may have indicated a decrease in the functional capacity of the cardiovenous system.

CASE 2.—M. S. was a woman, 40 years of age, who had the auscultatory signs of mitral stenosis and aortic incompetence. Her pulse was irregular. The blood pressure measured 110/50. There was venous engorgement in the neck, râles were heard over the basal portions of the lungs, the liver was slightly enlarged, and there was slight edema of the lower extremities. Roentgenologic examination showed that the heart was symmetrically enlarged. The electrocardiogram revealed auricular fibrillation and low voltage of the QRS complexes. The venous pressure at rest was slightly above normal; it showed a pronounced rise during exercise, and did not return to the initial level until three minutes after exercise (Fig. 3). Diagnoses: rheumatic

mitral stenosis and aortic incompetence, with clinical signs of congestive heart failure. The venous pressure readings and clinical manifestations were in agreement.

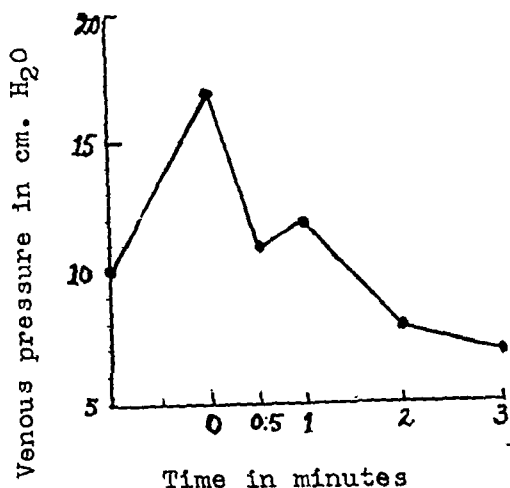


Fig. 2.

Fig. 2.—Normal venous pressure at rest. Pathologic response to exercise; pronounced rise and fall below the initial level.

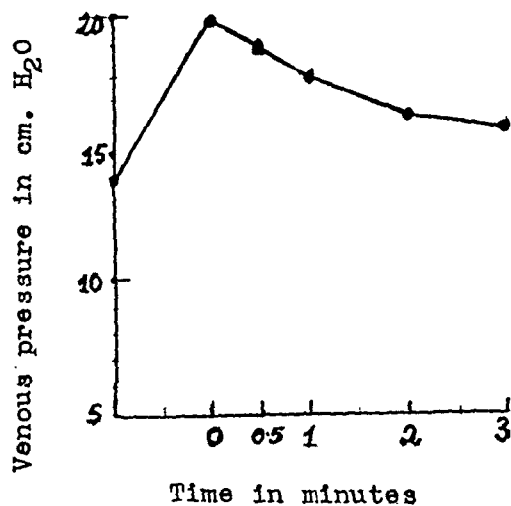


Fig. 3.

Fig. 3.—Slightly increased venous pressure at rest. No return to the initial level until three minutes. Evident pathologic response to exercise.

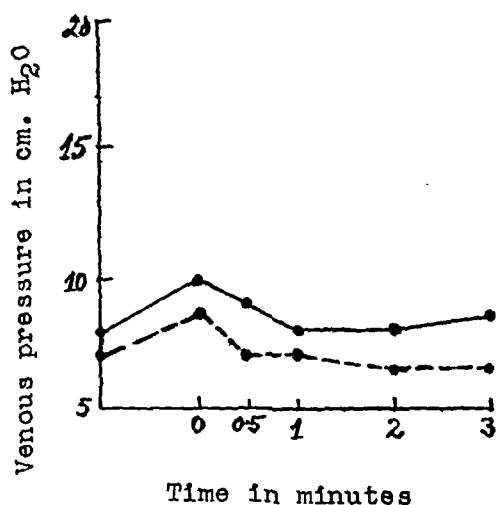


Fig. 4.—Normal venous pressure curve both during fibrillation (solid line) and sinus rhythm (dotted line).

CASE 3.—J. E. was a 39-year-old man who had auricular fibrillation without any evidence of a valvular lesion. There were no signs of congestive heart failure. The blood pressure was 120/80. Roentgenologically, the heart was normal in size and shape. The electrocardiogram showed auricular fibrillation, with normal ventricular complexes. The administration of quinidine abolished the auricular fibrillation. The venous pressure curve was normal both when he had fibrillation and after normal sinus rhythm had been restored (Fig. 4). Diagnoses: auricular fibrillation of uncertain etiology; no clinical evidence of congestive heart failure; normal venous pressure.

CASE 4.—J. G., a 45-year-old man, had auricular flutter and no clinical manifestations of congestive heart failure. The blood pressure was 115/80. Roentgeno-

logically, the heart was normal. An electrocardiogram which was made after cessation of the auricular flutter showed sinus rhythm, with T-wave inversion in the standard leads. The details of the venous pressure measurements are shown in Fig. 5. Diagnosis: paroxysmal auricular flutter, probably caused by coronary artery disease. The venous pressure was abnormally high at rest when flutter was present, and showed a pathologic response to exercise; after sinus rhythm became re-established the resting value was normal, and the response to exercise was nearly normal.

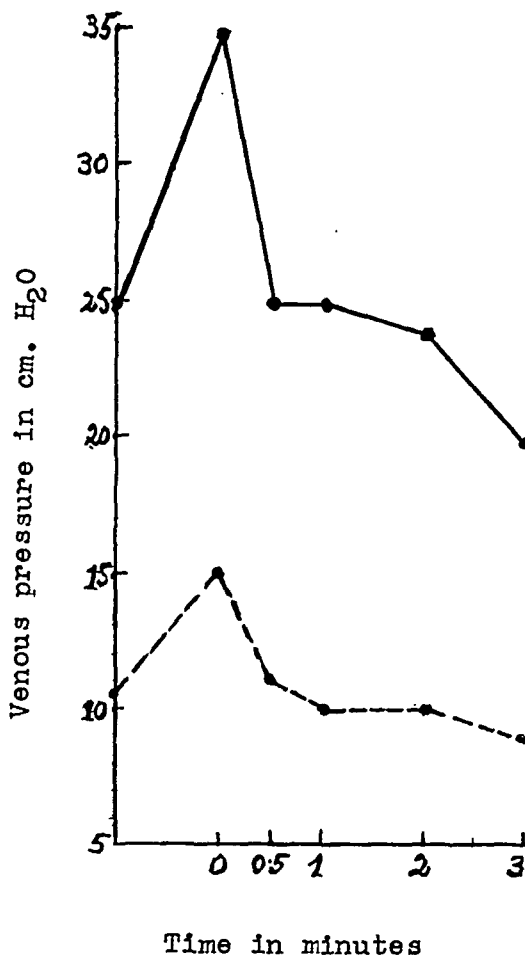


Fig. 5.—Pathologic venous pressure curve during auricular flutter (solid line). Nearly normal venous pressure curve during sinus rhythm (dotted line).

DISCUSSION

It is well known that exercise is accompanied by an elevation of the venous pressure. It may be emphasized that the degree of this elevation and the time necessary for the venous pressure to return to its basal level after exercise seem to be important factors in evaluating the functional capacity of the cardiovenous system.

In our normal subjects there was only a slight rise in venous pressure during exercise (about 1 to 4 cm. of water), and it reached its initial level within thirty seconds after exercise and never fell below it.

In some cases of heart disease without any clinical signs of congestive heart failure, the resting value was within normal limits, but in

the exercise experiment, after a rise of several centimeters of water, the venous pressure dropped below the initial level. White, Barker, and Allen⁷ and Nieuwenhuizen⁹ found that there was a slight fall below the basal level after exercise, not exceeding 1.5 cm. of water (Nieuwenhuizen), even in healthy young people. A greater fall below the original level was considered by Nieuwenhuizen as a pathologic reaction, and our observations support this view. It is open to question whether the fall of venous pressure below the initial level after exercise is due more to retrograde influences from the heart than to temporary changes in peripheral vascular tonus. Hooker¹¹ stated that local changes in vascular tonus caused no noticeable changes in venous pressure, and he concluded that venous pressure is normally independent of peripheral vascular resistance. The peripheral venous pressure is independent of factors affecting the peripheral vascular system or the blood flow therein, provided the heart is fully competent, as has been pointed out by Eyster and Middleton.¹² On the other hand, it is difficult to regard this fall of the venous pressure below the initial level after exercise as the result purely of some cardiac factor. We have observed it, however, only in cases of heart disease without clinical evidence of congestive failure. We believe that this response of the venous pressure to exercise may be explained by a decrease of the venous tonus in the presence of potential cardiac insufficiency.

In cases in which there was clinical evidence of congestive heart failure, the resting value was usually high, there was a considerable rise on exertion, and it took a longer time to return to the initial level than in normal subjects.

SUMMARY

The venous pressure, if measured only once, with the patient at rest, gives no satisfactory clinical information. The results of measuring the venous pressure during and after exercise enable one to make a more reliable evaluation of the functional capacity of the cardiovenous system.

The air-filled system for measuring the venous pressure with an aneroid manometer is a sound method, and is reliable enough for routine clinical use when technical precautions are strict.

The different types of venous pressure curves which were obtained in the exercise experiments are discussed.

I wish to express my gratitude to Professor Laubry, Head of the Cardiac Clinic, for his constant help and suggestions in the preparation of this paper. I also desire to thank Dr. John Parkinson of London, England, who kindly read the manuscript and made many suggestions for its improvement.

REFERENCES

1. Lyons, R. H., Kennedy, J. H., and Burwell, C. J.: The Measurement of Venous Pressure by the Direct Method, *AM. HEART J.* 16: 675, 1938.

2. Hooker, D. R.: The Effect of Exercise Upon the Venous Blood Pressure, *Am. J. Physiol.* 28: 235, 1911.
3. Schott, E.: Die Erhöhung des Druckes im venösen System bei Anstrengung als Mass für die Funktionstüchtigkeit des menschlichen Herzens, *Deutsches Arch. f. klin. Med.* 108: 537, 1912.
4. Villaret, M., Saint Girons, Fr., and Grellety-Bosviel, P.: La tension veineuse périphérique et ses modifications pathologiques, *Presse méd.* 31: 318, 1923.
5. Villaret, M., Saint Girons, Fr., and Justin-Besançon, L.: La Pression veineuse périphérique, Paris. Masson et Cie. 1930.
6. Bedford, D. E., and Wright, S.: Observations on the Venous Pressure in Normal Individuals, *Lancet* 2: 106, 1924.
7. White, H. L., Barker, P. S., and Allen, D. S.: Venous Pressure Responses to Exercise in Patients With Heart Disease, *AM. HEART J.* 1: 160, 1925.
8. Schneider, E. C., and Collins, R.: Venous Pressure Responses to Exercise, *Am. J. Physiol.* 121: 574, 1938.
9. Nieuwenhuizen, C. L. C.: Der venöse Blutdruck nach Arbeitsleistung. Eine Funktionsprüfung der Zirkulation, *Acta Med. Scand.* 103: 171, 1940.
10. Villaret, M., Saint Girons, Fr., and Guillaume, J.: Contribution à l'étude clinique de la tension veineuse. Technique et premiers résultats, *Compt. rend. Soc. de biol.* 84: 80, 1921.
11. Hooker, D. R.: Observations on the Venous Blood Pressure in Man, *Am. J. Physiol.* 35: 73, 1914.
12. Eyster, J. A. E., and Middleton, W. S.: Clinical Studies in Venous Pressure, *Arch. Int. Med.* 34: 228, 1924.
13. Olmer, D., Jouve, A. X., and Vague, J.: Une épreuve fonctionnelle de la circulation de retour, *Presse méd.* 2: 1233, 1938.

THE ACTION OF CALCIUM ON THE HUMAN ELECTROCARDIOGRAM

NORMAN E. CLARKE, M.D.
DETROIT, MICH.

THE continued response of heart muscle to stimuli depends upon calcium, and excessive amounts of calcium in a perfusion medium will completely suspend relaxation. Billigheimer¹ found that calcium makes the heart's contractile elements more powerful, i.e., that it has an inotropic and also perhaps a bathmotropic effect. After having performed experiments on animals, Kohn and Pick² believed that calcium paralyzed the auricles and increased the irritability of the ventricles. The cardiotonic action of calcium was investigated by Danielopolu, et al.,³ who thought that the diuresis which followed calcium therapy resulted from the action of the drug on the heart, but Loewenberg⁴ regarded the diuretic and cardiac effects as independent.

We have studied the action of calcium on the human heart with the electrocardiograph—a method used by Berliner.⁵ A 2 per cent solution of calcium chloride was used in most of our experiments, but in some a 10 per cent solution was used. From 45 to 75 grains of the drug were given intravenously over a period of three to twenty-one minutes. The rapidity of administration, or the concentration of the drug in the blood stream, determines the effect. One to four grams of calcium chloride were given intravenously by Ameuille and Rist⁶ in treating abdominal tuberculosis. The number of our experiments was limited because of the risk entailed by the doses we used, the difficulty of finding human subjects who were willing to undergo such experimentation, and our own reluctance to subject many to such a procedure.

A fairly constant train of symptoms was observed. The patients complained of intense flushing, or heat, palpitation increasing in intensity, a sense of oppression in breathing, nausea, a metallic taste, profuse perspiration, marked dyspnea, occasional vomiting, faintness, weakness, and a feeling of pressure over the upper sternum, with a dull general headache. Some of these symptoms are to be explained by the dynamic action of rapid intravenous administration.

Reports vary as to the effect of calcium on the blood pressure. We found, uniformly, an elevation of the systolic, and usually a depression of the diastolic, levels. These changes were transient; normal pressures

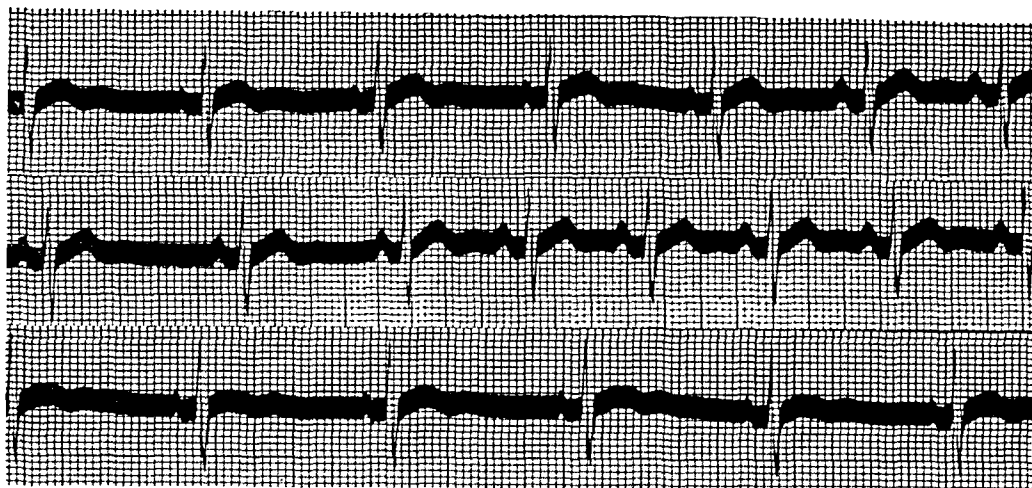


Fig. 1.—Case 1. Electrocardiogram shows sinus arrhythmia, slowing of the rate, and a decrease in the size of the P waves.

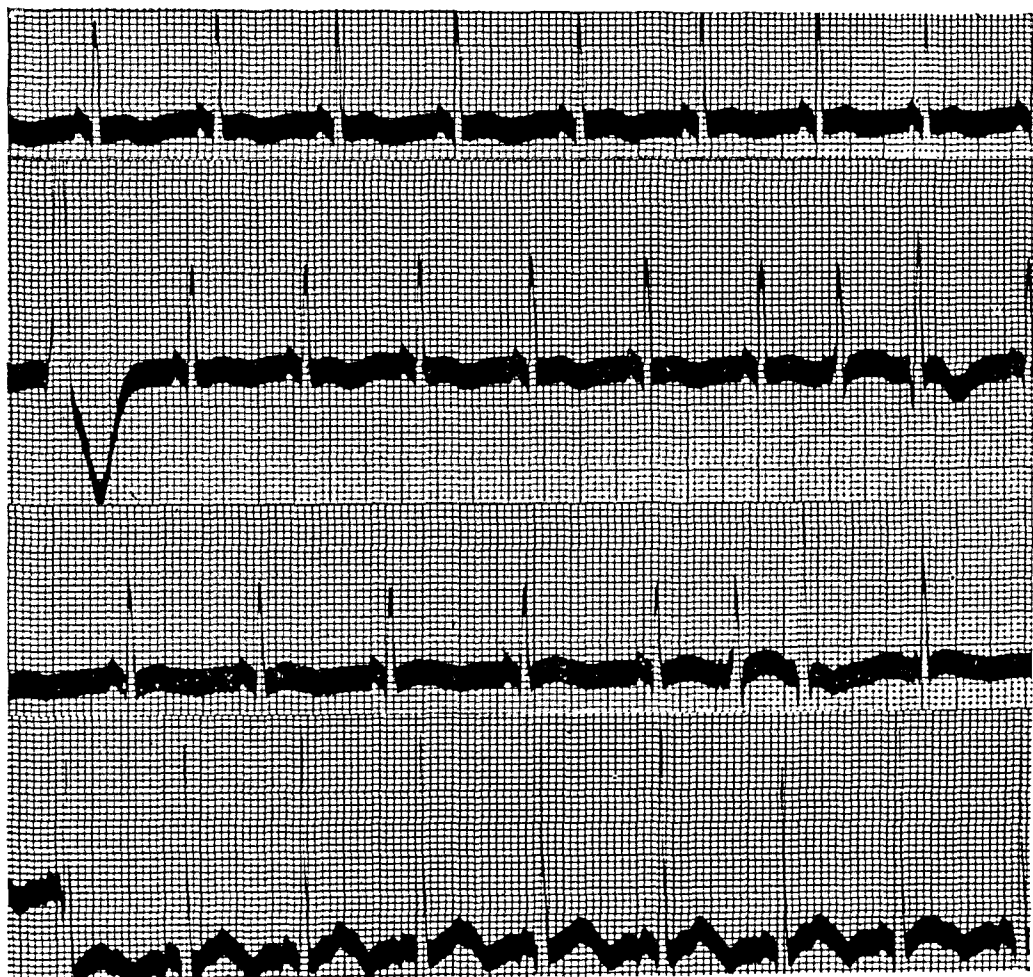


Fig. 2A.—Case 3. The heart rate is decreased; the P waves become smaller and occasionally are inverted; and ventricular extrasystoles of large voltage, and also auricular extrasystoles, appear. The size of the R waves is much increased; sinus arrhythmia is more pronounced, and the pacemaker shifts to a lower level.

returned within thirty minutes to one hour, and the maximum fall occurred within a few minutes after the administration of calcium was stopped.

CASE REPORTS

CASE 1.—A male physician, aged 34 years, who was in good health and had a normal heart, was the subject of our first and least satisfactory experiment. A total of 40 grains of calcium chloride in a 2 per cent solution was administered intravenously within twenty-one minutes. The appearance of palpitation, faintness, nausea, and vomiting required the discontinuance of the drug. There was no diuresis. The initial blood pressure was 135/80. The systolic readings during the administration of the calcium were 145 and 165, and the diastolic, 70 and 65, mm. Hg. The systolic pressure was 145, and the diastolic, 75, mm. Hg thirty minutes after the administration of calcium was stopped; the readings were normal within one hour. These changes were probably exaggerated by the anxiety associated with the procedure.

A continuous electrocardiographic record (Lead I) was made during the period of calcium administration (Fig. 1).



Fig. 2B.—Case 3. With further administration of calcium, sinoauricular and A-V block are present. Most of the P waves become inverted, and all are decreased in size. The P-P intervals are shorter, and the apices of the R waves are notched. An independent ventricular rhythm intervenes; the P waves are still present, with occasional ventricular response to the supraventricular stimulus.

CASE 2.—This was a man, aged 40 years, whose general health was good. This patient received 64.5 grains of calcium chloride by vein within eleven minutes. A 2 per cent solution was used. When 22.5 grains had been given, he complained of a metallic taste in his mouth and began to perspire profusely. There was no diuresis.

The normal, resting blood pressure was 95/65. During the injection of the calcium the systolic readings were 115, 125, 130, and 135, and the diastolic, 65, 65, 64, and 70 mm. Hg. Within twenty minutes after the withdrawal of the needle from the vein the blood pressure was 110/70. The electrocardiographic alterations were more pronounced than those shown by the first patient. The outlines were more distinct and the rate was decreased, but sinus arrhythmia was not so evident. The P waves were decreased in size, and became inverted, with a sharpening of their apices.



Fig. 2C.—Case 3. The heart rate becomes more rapid; the size of the R waves remains much increased, and all evidence of auricular activity disappears.

CASE 3.—This patient, aged 45 years, had a chronic discharging sinus on his left leg. The cardiovascular examination showed nothing abnormal. He was given 250 c.c. of a 2 per cent solution of calcium chloride (75 grains) within nine minutes by the intravenous route. There were few symptoms. The tracings are chest leads; Lead II was used for the continuous tracing. The normal, resting blood pressure was 145/90. During the administration of the calcium the systolic readings were

150, 150, 180, and 175, and the diastolic, in the same sequence, were 85, 80, 80, and 75 mm. Hg. The striking changes in his electrocardiograms are shown in Fig. 2*A*, *B*, *C*, *D*.

In Case 3 the heart rate decreased; sinus arrhythmia appeared; the pacemaker was displaced to a lower level; and transient partial and complete heart block was produced. These changes resemble those produced by vagal stimulation. It was observed by Hoff and Nahum,⁷ in their experimental work with rabbits, that suppression of vagal action by atropine before the intravenous injection of calcium prevented A-V delay and auricular fibrillation.



Fig. 2*D*.—Case 3. In the first half of this series the P waves are again evident; some are upright, and others are inverted. In the last half, the idiopathic ventricular rhythm resumes, with a short period of bigeminal rhythm; the extrasystoles are of the same form as those in the paroxysm.

That there is an action on the ventricular muscle seems probable; extrasystoles, usually of large voltage, and series of extrasystoles or paroxysmal ventricular tachycardia occur. This type of extrasystole persists when the vagus is suppressed by atropine, according to Hoff and Nahum,⁷ which suggests that increased ventricular excitability is produced by direct calcium action on the ventricular muscle.

In an effort to further differentiate the vagal and direct muscle action of calcium chloride, we administered the drug to a patient with auricular fibrillation.

CASE 4.—A man, aged 47 years, with rheumatic heart disease, had had heart failure with dependent edema, for five months. He had cardiac enlargement, auricular fibrillation, and mitral stenosis. He had received a small amount of digitalis previous to the administration of 45 grains of calcium chloride in a 10 per cent solution, intravenously, within three minutes.

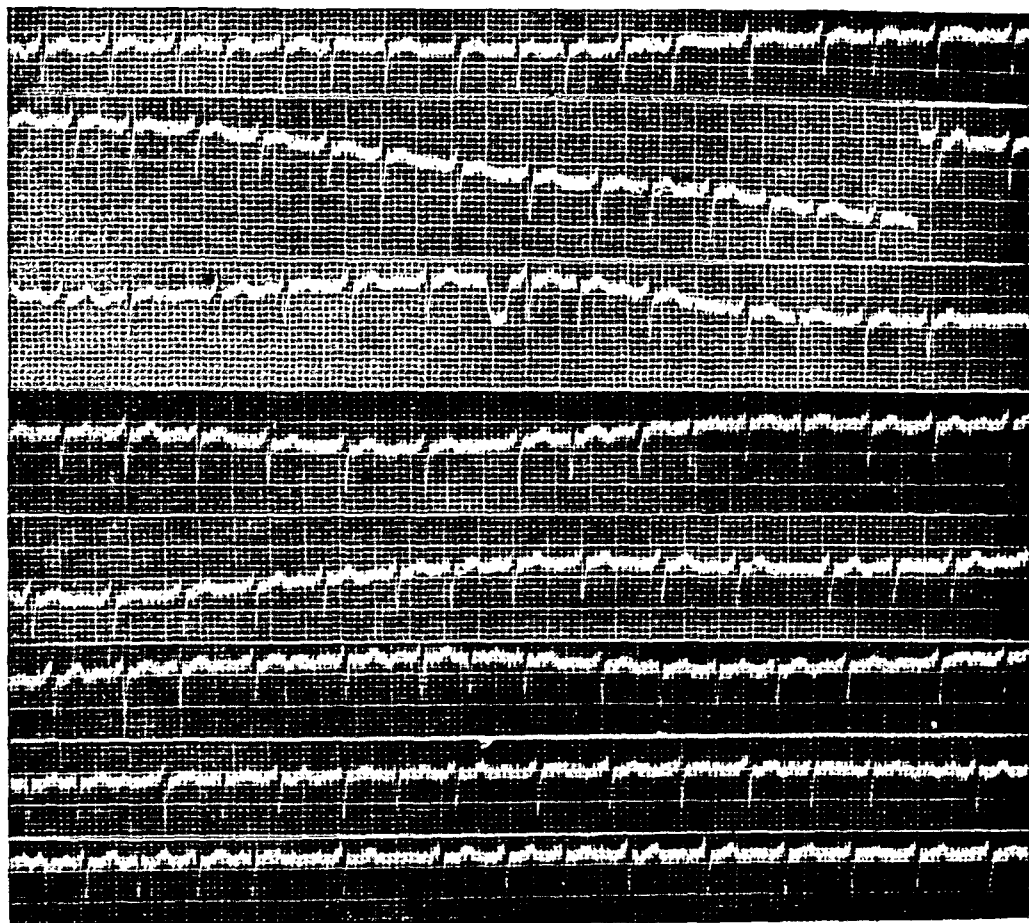


Fig. 3.—Case 4. Lead I was used. This continuous record was taken during intravenous administration of the calcium solution, but no change is noted in the electrocardiogram.

In this single experiment, the calcium had no detectable effect on the electrocardiogram, i.e., the changes which were noted in cases of sinus rhythm did not occur in the presence of auricular fibrillation. A single example does not permit conclusions.

SUMMARY

The intravenous therapeutic use of calcium has advantages and benefits, but carries definite danger.

Calcium produces changes in the human electrocardiogram which are progressive and depend upon the calcium concentration in the blood stream.

The earliest and vagus-like actions are bradycardia, sinus arrhythmia, shifting of the pacemaker, and various degrees of heart block.

Calcium may act directly upon the ventricular muscle, increasing its excitability, and producing foci of idiopathic ventricular rhythm and ventricular extrasystoles of large and unusual form.

The blood pressure was altered; the systolic level was raised, and the diastolic usually was depressed. Accompanying psychic factors and symptoms, such as nausea and chest oppression, could account for some of the change.

We observed no diuresis from calcium administration, and the effects on the heart itself were very transitory.

In the single case of auricular fibrillation the intravenous administration of calcium had no effect on the electrocardiogram.

REFERENCES

1. Billigheimer, E.: Vergleichende Untersuchungen über die Wirkung und Wirkungsweise des Calciums und der Digitalis, *Ztschr. f. klin. Med.* 100: 411, 1924.
2. Kolm, R., and Pick, E. P.: Über die Bedeutung des Kaliums für die Selbststeuerung des Herzens, *Arch. f. d. ges. Physiol.* 185: 235, 1920.
3. Danielopolu, D., Draganesco, S., and Copaceanu, P.: Les sels de calcium dans l'asystolie, *Presse méd.* 30: 413, 1922.
4. Loewenberg, B.: L'action cardiotonique et l'action diurétique du chlorure de calcium, *Ann. de méd.* 13: 172, 1923.
5. Berliner, K.: Effect of Calcium Injections on the Human Heart, *Am. J. M. Sc.* 191: 117, 1936.
6. Ameuille, P., and Rist, E.: Les injections intraveineuses de chlorure de calcium, *Bull. et mém. Soc. méd. d. Hôp. de Paris* 48: 531, 1924.
7. Hoff, H. E., and Nahum, L. H.: An Analysis of the Cardiac Irregularities Produced by Calcium, and Their Prevention by Sodium Amytal, *J. Pharmacol. & Exper. Therap.* 60: 425, 1937.

EXPERIMENTAL STUDIES ON THE EFFECT OF TEMPORARY OCCLUSION OF CORONARY ARTERIES

II. THE PRODUCTION OF MYOCARDIAL INFARCTION

HERRMAN L. BLUMGART, M.D., D. ROURKE GILLIGAN, M.S., AND
MONROE J. SCHLESINGER, M.D.
BOSTON, MASS.

CLINICAL and post-mortem observations suggest that temporary, relative ischemia in the heart may lead to myocardial necrosis and persistent electrocardiographic changes characteristic of myocardial infarction.¹⁻⁴ In cases of angina pectoris caused by coronary arteriosclerosis, small areas of myocardial fibrosis are at times found at autopsy in the presence of narrowing, but without occlusion, of the arteries supplying the affected area. In accord with these observations is the fact that patients during attacks of angina pectoris usually show temporary electrocardiographic changes of the type seen in myocardial infarction.

The experimental investigation reported here was designed to ascertain the duration of the localized ischemia caused by temporary occlusion of a coronary artery which is necessary to produce myocardial infarction in the dog. The effect of temporary myocardial ischemia on the electrocardiogram of the cat has been reported previously,⁵ and further electrocardiographic observations on dogs are reported here.

Considerable information is available concerning how long anoxia must last in order to cause permanent damage in various parts of the nervous system⁶⁻⁸; almost no exact information is available, however, regarding the period of ischemia required to produce irreversible myocardial changes.

MATERIAL AND METHODS

Temporary arrest of blood flow by occlusion of a coronary artery for 3.5 to forty-five minutes was performed on thirty-four dogs. In five control experiments the same operative procedure was carried out, with the only exception that actual occlusion was not practiced. In two additional dogs a coronary artery was permanently occluded.

From the Medical Research and Pathology Laboratories, Beth Israel Hospital, and the Departments of Medicine and Pathology, Harvard Medical School.

Some of the observations reported herein were presented at the Fifty-Second Session of the Association of American Physicians, May, 1937.

This investigation was aided by grants from the Proctor Fund for the Study of Chronic Diseases, Harvard Medical School, and from the Josiah Macy, Jr., Foundation, New York.

Received for publication Jan. 6, 1941.

Operative Procedure.—All operations were performed under aseptic precautions. Anesthesia was produced by intravenous injection of a solution of nembutal in the amount of 35 to 40 mg. of nembutal per kilogram of body weight. In a few animals, small amounts of ether also were required during the course of the experiment.

With the dog anesthetized and on artificial respiration, the heart was exposed through an intercostal incision at the fourth interspace. The left circumflex coronary artery was approached from the right side of the chest; the left anterior descending coronary artery, from the left side of the chest.

A small pericardial incision was made over the site of the artery to be tied. The heart was brought into a favorable operative position by slight traction on hemostats placed on the opened edges of the pericardium. The lung in the immediate operative field was protected during dissection of the artery by a sponge soaked with saline. The coronary artery was carefully and quickly freed from adjacent tissue over an area of 2 to 3 mm., and a No. 2 catgut ligature was slipped loosely beneath it. Veins adjacent to the artery were never included in the ligature. The heart was allowed to drop back into the chest and was kept moist with saline. Traction on the ligature placed beneath the artery was exerted gently to the point of complete occlusion of the artery and was maintained for periods varying from 3.5 to forty-five minutes. Then the ligature was removed and the artery massaged for a few seconds. The color, force of contraction, and degree of dilatation of the heart were observed during the entire procedure. The pericardial incision was sutured in all but the first few animals, and the chest was closed. An injection of 200 to 400 c.c. of 5 per cent glucose in physiologic saline solution was given intraperitoneally.

Leads I, II, and III of the electrocardiogram were taken before operation. In some experiments, additional tracings were taken during various phases of the operative and occlusive procedures. In all cases, the three leads were taken at the end of the operation, again a few hours later, and at intervals of one to three days until the animal was sacrificed. A No. 2 Hindle electrocardiograph was utilized.

The animals were sacrificed from five hours to forty days postoperatively. With the animal under nembutal anesthesia, the chest was re-opened and the heart was removed intact in the pericardium. The pericardium was removed on the dissecting table; adhesions of the pericardium to the heart at or near the operative site were observed in approximately one-half of the experiments, both in the control group and in the group in which temporary occlusion of an artery had been made. In every instance the artery which had been occluded temporarily was carefully probed past the point where the ligature had been passed. The artery and its branches were then laid open as far as possible and examined, frequently under the dissecting microscope. In two animals the lumen of the artery was found narrowed at the point of traction; these experiments were discarded. In the reported cases, including both the control cases and those in which temporary occlusion was practiced, the lumen of the artery which had been temporarily occluded contained no thromboses, fresh or organized, showed no narrowing at the operative site, and the intima was smooth and glistening throughout the entire observable length. Likewise, no obstruction was found in the other main arteries in any animal.

The heart was examined over its entire epicardial surface for macroscopic evidences of pathologic changes, and was laid open for examination of the endocardium. Frequent parallel cuts were then made through the cardiac musculature, and the surfaces of these carefully examined.

Blocks of tissue were removed for microscopic study from the area of the myocardium supplied by the artery which had been temporarily occluded, and also from a portion of the ventricle supplied by another main coronary artery; these latter blocks served as a control.

RESULTS

Control Experiments

In five control experiments the entire operative procedure was performed, with the exception that the ligature, after being placed beneath the artery, was removed after several minutes without occlusion of the vessel. The animals were sacrificed from one to thirty-five days postoperatively (Table I).

Electrocardiographic Observations.—Changes in the direction of the T waves of Leads II and III from upright before operation to inverted in one or more of the postoperative tracings occurred in four of the five control experiments; in the fifth (Dog 68), T_2 and T_3 were inverted preoperatively and showed a greater degree of negativity postoperatively. The S-T segment of Leads II and III changed from the isoelectric level of the preoperative tracings to +1.0 or +1.5 mm. in four of the experiments, and to -1.0 mm. in the fifth (Dog 65). Similar changes have been reported by others.^{9, 10} No ectopic beats were observed in any of the tracings.

Morphologic Observations.—No gross or microscopic evidences of cardiac infarction were found in any of the five control experiments (Table I). Further, in none of the hearts were there any evidences of lesions in the control areas supplied by intact arteries.

Temporary Occlusion Experiments

Occlusion of a coronary artery for 3.5 to forty-five minutes was performed on thirty-four dogs. Within the first minute of occlusion of an artery, the myocardium supplied by it appeared cyanotic, and the force of contraction of this area soon diminished. Dilatation of the affected cyanotic area was obvious during the latter part of the longer occlusions. Irregularities of the heartbeat were observed frequently. On re-establishment of blood supply, the affected myocardium quickly resumed its normal color. Normal pulsation and reappearance of normal color of the artery distal to the point of occlusion were observed invariably.

Extrasystoles and Ventricular Fibrillation.—In approximately one-half of the experiments, isolated ventricular extrasystoles occurred during occlusions, or within the first few minutes after re-establishment of blood flow. In several experiments, isolated extrasystoles were seen in electrocardiograms which were taken on postoperative days.

Ventricular fibrillation, with subsequent death, occurred in eight animals; in four of these, fibrillation developed during the first five minutes of occlusion, and, in the other four, within a few seconds after re-establishment of blood flow following occlusions lasting fifteen and thirty minutes (Table I). In seven of these animals the left

TABLE I
EFFECTS OF TEMPORARY CORONARY ARTERIAL OCCLUSION ON DOGS

DOG NO.	ARTERY OCCLUDED	DURATION OF OCCLUSION (MIN.)	PERSISTENT ELECTRO-CARDIO-GRAPHIC ABNORMALITIES*	DURATION OF ELECTRO-CARDIO-GRAPHIC ABNORMALITIES (DAYS)	SACRIFICE OF ANIMAL (TIME POSTOPERATIVELY)	MYOCARDIAL LESIONS	
						GROSS EVIDENCES†	MICROSCOPIC EVIDENCES
<i>Animals Sacrificed 4 to 40 Days Postoperatively</i>							
14	LC	5	+	4	4 days†	0	-
15	LC	10	0		34 days	0	0
17	LC	10	0		40 days	0	0
13	LC	10	+	11	11 days	0	0
7	LAD(B)	20	+	22	22 days	0	0
19	LC	20	+	12	34 days	0	+
21	LC	20	+	2½	4 days†	0	
22	LC	25	+	10	22 days	+	+
23	LC	30	0		22 days	+	+
3	LAD	30	0		8 days	0	0
9	LAD(B)	30	+	14	14 days	+	+
26	R(B)	35	+	7	13 days	0	+
8	LAD(B)	40	+	18	18 days	+	+
29	LC	45	0		7 days	++	+
27	LC	45	+	10	13 days	++	+
53	LC	45	0		14 days	0	0
54	LC	45	+	14	17 days	++	+
55	LC	45	+	16	16 days	++	+
<i>Sacrificed 4.5 to 28 Hours Postoperatively</i>							
51	LC	15	0		20 hours	Edema	0
52	LC	15	+		28 hours	Edema	0
58	LC	20	0		24 hours	0	0
61	LC	20	0		26 hours	0	+
62	LC	30			4.5 hours	0	0
63	LC	15			5 hours	0	0
69	LC	45			4.5 hours	0	0
70	LC	45			4.5 hours	0	0
<i>Died of Ventricular Fibrillation During Operation</i>							
24	LC	3½					0
18	LC	4					0
59	LC	4½					0
20	LC	5					
12	LC	15					0
28	LC	15					0
50	LC	15					0
10	LAD(B)	30					0
<i>Control Experiments</i>							
65	LC§		0		1 day	0	0
67	LC§		0		1 day	0	0
68	LC§		0		6 days	0	0
66	LC§		0		13 days	0	0
16	LC§		0		35 days	0	0

LC, left circumflex artery; LAD, left anterior descending; R, right artery; B, branch of a main coronary artery.

*In this analysis, + signifies electrocardiographic changes characteristic of myocardial ischemia of a character and degree not observed in control experiments. See text for changes in controls which are tabulated here as 0.

†Animal died.

‡+ signifies one to numerous tiny areas (2 to 4 mm. in diameter) of fibrosis; ++ signifies fibrotic areas of considerable size up to ½ left ventricle grossly included.

‡Last electrocardiogram taken before death.

§Ligature placed under artery and withdrawn without occluding artery.

circumflex artery had been occluded, and in one, a branch of the left anterior descending artery. Isolated ventricular extrasystoles during the period of occlusion occurred more frequently in animals which subsequently developed ventricular fibrillation.

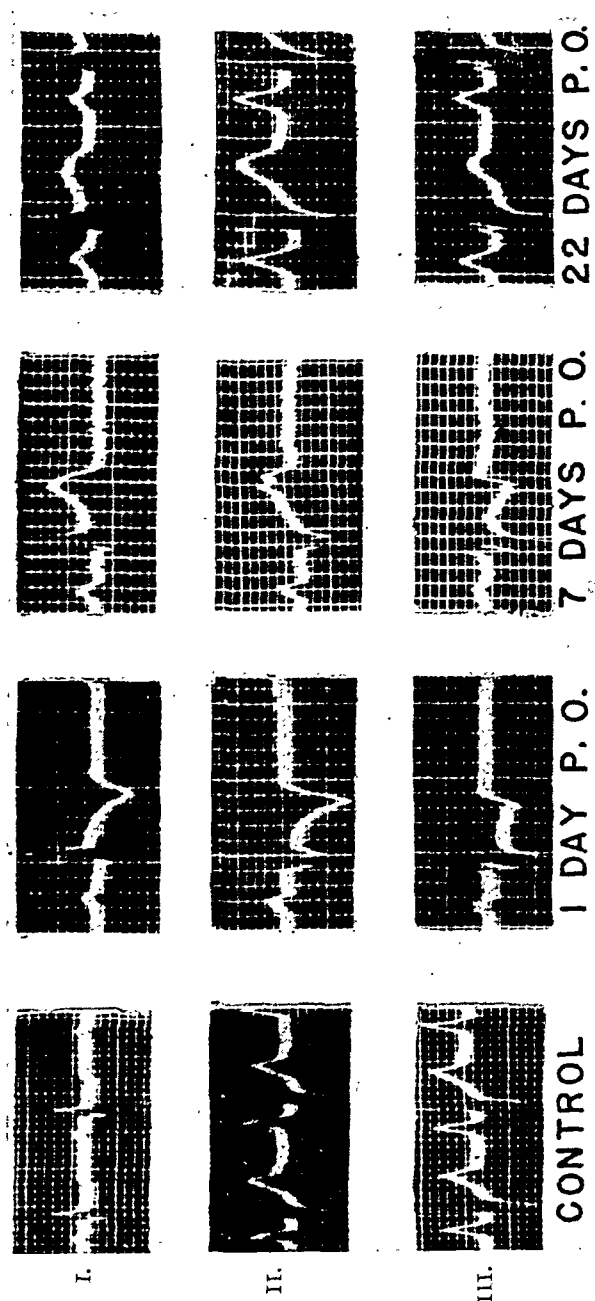


Fig. 1.—Dog 7. Electrocardiograms taken before, and one, seven, and twenty-two days after, a twenty-minute occlusion of a branch of the left anterior descending coronary artery.

Electrocardiographic Changes.—Twelve of the eighteen dogs on which electrocardiograms were made during the postoperative period of four to forty days showed persistent changes typical of myocardial ischemia and different in character and degree from those which occurred in any of the control experiments (Table I). They consisted in more marked aberrations of the S-T segment, with coving, notching, and

other deviations in QRS complexes, and extrasystolic irregularities (Figs. 1, 2, and 3). The maximum changes in the S-T segment usually were observed during the first to fourth postoperative days; the changes persisted for several days to weeks after operation. The type, anterior or posterior, of these electrocardiographic changes varied, depending upon which artery was occluded (Figs. 1, 2, and 3).

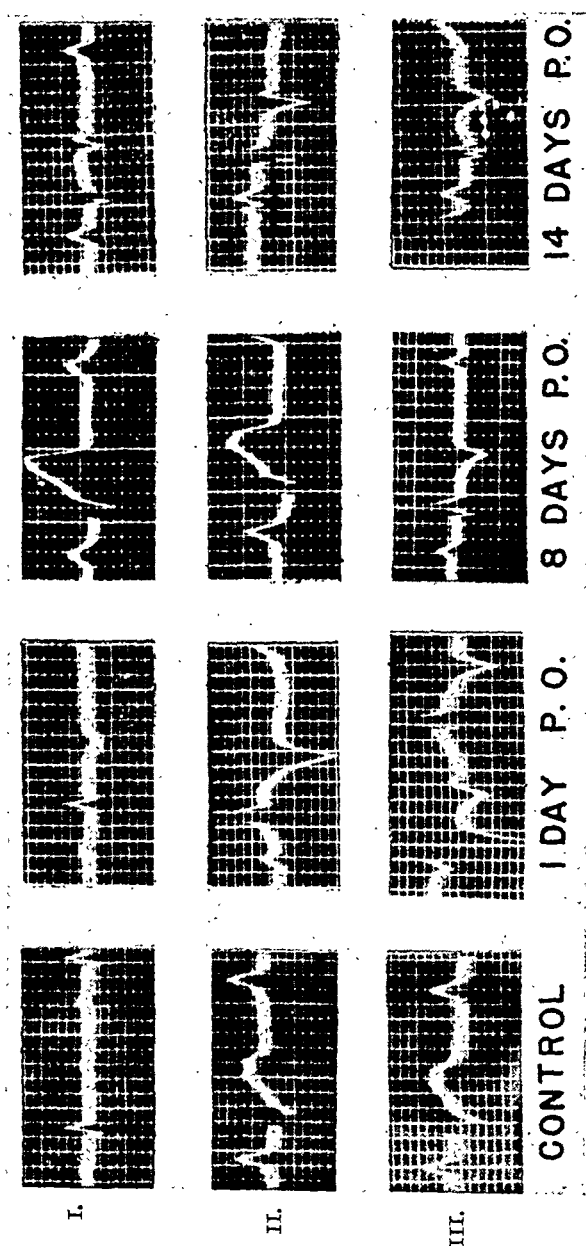


Fig. 2.—Dog 8. Electrocardiograms taken before, and one, eight and fourteen days after, a forty-minute occlusion of a branch of the left anterior descending coronary artery.

The occurrence of these postoperative electrocardiographic changes was related neither to the duration of occlusion, as produced in these experiments, nor to the presence or absence of an infarct. Although eight of the ten animals which developed myocardial lesions likewise

showed electrocardiographic changes in one or more of the standard three leads, four of the eight whose hearts were free from pathologic changes showed similar electrocardiographic abnormalities. It is important in this connection that all of the animals in which occlusion was produced showed changes in the T wave and S-T segment, but that only the changes which were different from, or much greater than, those observed in any of the control experiments were considered as definitely due to the effects of occlusion.

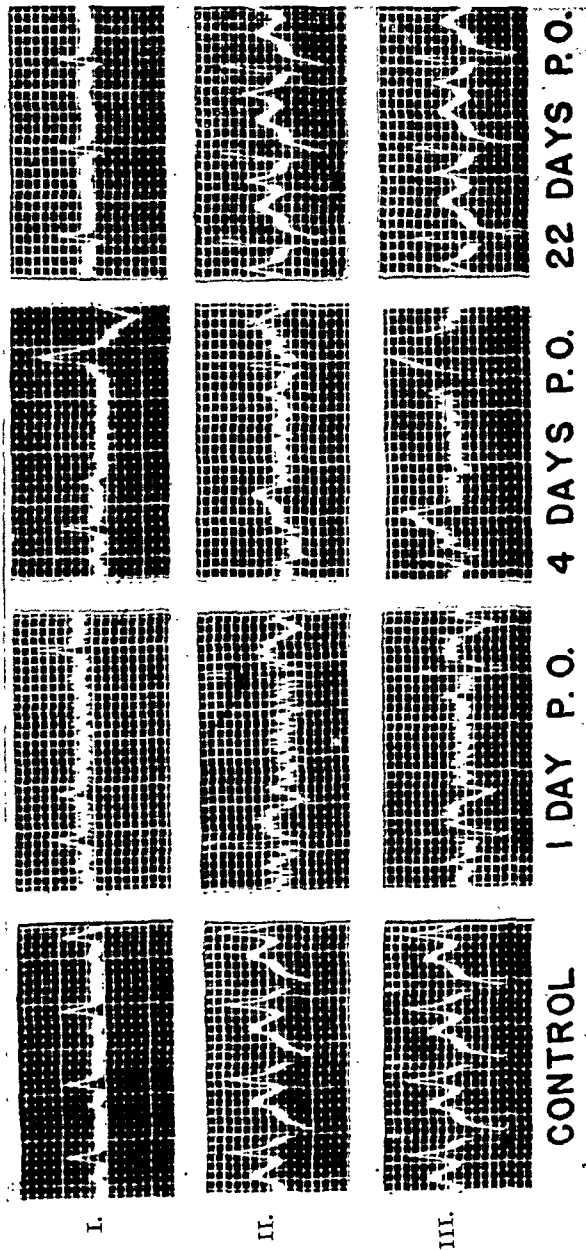


Fig. 3.—Dog 22. Electrocardiograms taken before, one, four, and twenty-two days after, a twenty-five-minute occlusion of the left circumflex coronary artery.

Pathologic Changes.—Myocardial lesions were usually not detectable, either by gross or microscopic examination, in those dogs which were sacrificed from 4.5 to twenty-eight hours after temporary arterial

occlusions lasting fifteen to forty-five minutes. No gross or microscopic evidences of myocardial lesions were found in six of the hearts of the seven dogs which were subjected to temporary occlusion of the coronary artery for twenty minutes or less, and survived for four or more days. In the one exception (Dog 19) the artery had been occluded for twenty minutes, and the animal was sacrificed thirty-four days later. This myocardium showed a few, tiny, fibrotic scars which were detected only microscopically.

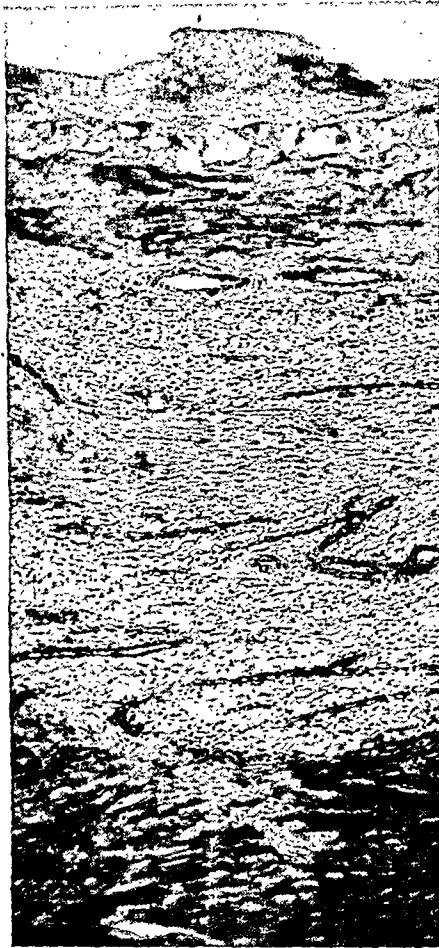


Fig. 4.—Dog 8. Photomicrograph of portion of myocardium supplied by a branch of the left descending coronary artery which had been occluded for forty minutes eighteen days before sacrifice of the animal. Note portions of several large areas in a healing infarct, with collapse of the vascular stroma subsequent to the loss of myocardial fibers. These areas are infiltrated with pigment-laden monocytes and lymphocytes. An organized endocardial thrombus is present.

Only two hearts with no evidences of myocardial lesions (Table I, Dogs 3 and 53) were found among the eleven dogs in which the temporary occlusion had been maintained for twenty-five or more minutes and the dogs allowed to survive for seven or more days. In the other nine hearts of this group, myocardial damage was found in the area supplied by the artery which had been temporarily occluded; in one heart, only microscopic lesions were noted (Dog 26); in the other eight

(Table I), the lesions were readily detected on gross examination. In four hearts (Dogs 8, 9, 22, and 23), in which the occlusion had been maintained for twenty-five to forty minutes, the lesions consisted of one to numerous tiny areas (2 to 4 mm. in diameter) of gray, depressed tissue embedded in the myocardium. In the other four hearts (Dogs 27, 29, 54, and 55), however, in which the occlusion had lasted forty-five minutes, an area of considerable size, amounting to as much as one-third of the left ventricle, appeared, grossly, to be involved. Such large regions usually had fairly well-defined borders and appeared swollen, yellowish, and more opaque than the unaffected myocardium.

The gross evidences of myocardial damage were in each instance confirmed by the microscopic examination. In general, the microscopic characteristics were similar to those which are seen after permanent ligation of the coronary artery of the dog. The time relations between the various microscopic changes and the interval after operation agreed closely with those observed by Mallory, White, and Salcedo-Salgar¹¹ in their study of human cardiac infarcts. The type of lesion which was found after forty minutes of occlusion and eighteen days' survival is shown in Fig. 4. In some of these hearts (Dogs 8, 27, 29, 54, and 55), a lesion was found which the above authors did not describe, and which we have not noted in infarcts in human hearts. This lesion consisted of an outlining by calcium deposition of the structural details of isolated, individual, myocardial fibers.

COMMENT

Myocardial and Electrocardiographic Changes Which Result From Experimental, Temporary, Coronary Occlusion

Previous studies in this laboratory showed that temporary myocardial ischemia in cats, produced by occlusion and subsequent reopening of the left anterior descending coronary artery, causes electrocardiographic changes which persist for days after re-establishment of the blood supply.^{5, 12} The postoperative electrocardiographic changes were usually of the anterior infarction type, corresponding to the vessel temporarily occluded, and were similar to those observed during occlusion. As reported here, occlusion of a coronary artery in dogs for periods of five to forty-five minutes also usually caused electrocardiographic changes which persisted for days to weeks; there was no close relation between the degree of electrocardiographic change and the magnitude of the myocardial lesion.

In the earlier studies, none of the cats in which temporary coronary occlusion was maintained for periods of five to thirty-five minutes showed gross or microscopic evidences of cardiac infarction which could be attributed to the temporary ischemia.⁵ In many of the hearts of the control cats, as well as of the experimental animals, microscopic examination

revealed small fibrotic lesions scattered throughout the myocardium.⁵ For this reason, dogs, in which spontaneous myocardial lesions were not encountered, were chosen for a continuation of these studies. The duration of the arterial occlusion was lengthened, and the postoperative survival period was increased. In dogs, coronary arterial occlusions lasting twenty-five to forty-five minutes usually resulted in grossly detectable myocardial lesions, whereas, after occlusions of twenty minutes or less, gross myocardial lesions were never found, and microscopic fibrosis was found in but one heart. That myocardial infarction did not occur in cats after periods of occlusion similar to those which resulted in lesions in the dog may be due to species differences in the distribution of, and blood flow in, the coronary arteries and their branches.

Tennant, et al.,^{13, 14} produced temporary occlusion of a coronary artery and its accompanying veins in dogs, and found that no permanent myocardial damage resulted when the period of occlusion varied from five to thirty minutes, but did find myocardial lesions after two- to eight-hour occlusions. Fauteux¹⁵ has noted that permanent occlusion of a coronary artery in dogs results in smaller myocardial lesions if the veins draining the area supplied by the occluded artery have been previously ligated. The absence of venous congestion in our experiments may explain why myocardial lesions occurred after a shorter period of arterial occlusion than in Tennant's^{13, 14} experiments. It is of interest that Bronson¹⁶ found focal myocardial fibrosis in one dog which was sacrificed one month after a coronary artery had been occluded for thirty minutes; in this experiment, as in those of the present study, the veins accompanying the artery were not occluded.

Chemical Changes in the Myocardium

Because of the absence of detectable morphologic alterations in the myocardiums of animals which were sacrificed soon after temporary coronary artery occlusion, studies were made to ascertain whether there might be chemical abnormalities of the affected myocardial tissue. The hearts of eight dogs were examined after occlusions lasting fifteen to forty-five minutes and re-establishment of blood flow for five to twenty-eight hours before the animals were sacrificed (Table I).^{17, 18} From the results of quantitative analyses of the sodium, chloride, potassium, and water content of that part of the myocardium supplied by the temporarily occluded artery, it was concluded that these temporary occlusions gave rise early to an extracellular edema amounting to as much as 10 per cent of the volume of extracellular fluid, or that as much as 2.5 per cent of the intracellular phase became permeable to chloride and sodium.^{17, 18}

Comparison of the Vulnerability of the Myocardium and of the Central Nervous System to Anoxia

The vulnerability of the myocardium to anoxia, as disclosed by these electrocardiographic,⁵ chemical,^{17, 18} and morphologic studies, is

strikingly analogous to that of the central nervous system.^{6, 19-21, 25} When the myocardium of the cat is deprived of its blood supply, electrocardiographic changes and loss of contractility appear in less than sixty seconds; cerebral anemia lasting twenty seconds obliterates the usual action potentials of the cerebral cortex of the cat.²² Twenty or more minutes of temporary ischemia are required to produce myocardial necrosis in the dog; this is comparable to the periods of anoxia of ten or more minutes which are required to produce histologic changes in the cerebrum of the cat⁷ and to the periods of fifteen or more minutes that are required to produce irreversible changes in the cerebrum of the dog.²³ That various parts of the brain differ considerably in their sensitivity to anoxia has been demonstrated by Heymans and his associates.^{20, 21} In contrast to the susceptibility of the heart and central nervous system to anoxia, the intestine can be deprived of its blood supply for as long as three hours without producing irreversible changes in the nerve cells of the myenteric plexus.²⁴

Comment on the Relation of Experimental Results to the Clinical and Pathologic Manifestations of Coronary Artery Disease

The above-described experiments were undertaken to elucidate certain clinical problems, as well as to provide information regarding the physiology and pathology of the myocardium. In a recent communication dealing with the relation of the clinical manifestations of angina pectoris, coronary thrombosis, and myocardial infarction to the pathologic findings,¹ it was repeatedly emphasized that the clinical and pathologic data indicated that myocardial ischemia is responsible for cardiac pain. That the heart may recover without structural damage if the duration and degree of ischemia are not too great is amply attested by the symptomatology, electrocardiographic studies, and pathologic findings. If, however, the degree and duration of myocardial ischemia are sufficiently great, irreversible damage, i.e., myocardial necrosis, with its associated symptomatology, results. The duration of temporary occlusion which is necessary to produce structural lesions in the anesthetized normal dog should not be understood as applying quantitatively to the diseased heart of man. The presence or absence of arteriosclerotic narrowing and of collateral circulatory pathways, and conditions such as exercise, anemia, and thyrotoxicosis, in which the heart is performing considerable work, influence materially the degree and duration of ischemia which the myocardium can tolerate. When the cardiac work is increased or the coronary blood supply is decreased, periods of ischemia shorter than those required in our animal experiments would presumably cause myocardial lesions. In man, pathologic observations indicate that inadequacy of the blood supply over a prolonged period of time may cause the same myocardial changes as complete ischemia of shorter duration.¹ In the animal experiments, this concept was substantiated by the fact

that the larger infarcts were produced only by the longer periods of occlusion (Table I), presumably because the peripheral regions of the myocardium which were deprived of their normal blood supply derived an additional supply from neighboring sources.^{26, 27}

Experimental, Clinical, and Pathologic Data in Relation to Angina Pectoris.—The focal areas of fibrosis that commonly are found in the hearts of patients with angina pectoris, and in those areas of the hearts of dogs which have been subjected to temporary ischemia for approximately twenty to thirty-five minutes, would seem to have a common underlying pathologic physiologic mechanism. It is the consensus that angina pectoris is the clinical expression of temporary, relative, myocardial ischemia. The electrocardiographic changes during attacks are similar to those induced by the inhalation of low-oxygen mixtures in man,²⁸ and to those observed in animals in which temporary circulatory arrest is produced by traction on a coronary artery.²⁹ As noted above, it is not to be expected that a close quantitative relation between the experimental observations and clinical conditions, in respect to duration and degree of ischemia, should obtain.

Experimental, Clinical, and Pathologic Data in Relation to Coronary Failure.—Some patients have cardiac pain more prolonged than that consistent with a diagnosis of angina pectoris, but the clinical evidences of myocardial necrosis, such as fever, leucocytosis, markedly increased sedimentation rate, or progressive electrocardiographic changes over a period of days, are absent. If death, in such cases, is not caused by heart disease, autopsy shows no evidence of myocardial infarction. Since these attacks are more prolonged than those of angina pectoris, and, on the other hand, since the signs of widespread myocardial necrosis are absent, a clinical diagnosis of either angina pectoris or acute myocardial infarction would be erroneous. Coronary failure and angina pectoris seem to have the same physiologic basis, i.e., completely or almost completely reversible myocardial changes caused by ischemia. That these attacks may leave their mark in the form of tiny foci of myocardial necrosis is suggested not only by the pathologic findings, but also by the observations of Riseman and Brown,³⁰ who found that the sedimentation rate of such patients, while not elevated as much as with myocardial infarction, is nevertheless definitely above the upper limits of normal.

Experimental, Clinical, and Pathologic Data in Relation to "Silent Infarction" of the Myocardium.—Various authors have commented on the finding of infarcts at post-mortem examination in the absence of any history of corresponding clinical phenomena.^{2, 31, 32} An inaccurate history as the result of a lapse of memory on the part of the patient, or absence of pain because the patient had been "unsensitive" is frequently postulated. Our experimental results, as well as pathologic observations by one of us (M. J. S.), suggest a somewhat different explanation in certain instances.^{1, 33} Some hearts (Blumgart, et al.,¹ Cases 4,

9, 10, 11, 19, and 20) show areas of fibrosis which are larger than the diffusely distributed small foci of fibrosis commonly associated with angina pectoris. These areas generally are regarded as healed infarcts. In most of the instances studied by us, however, the vessels leading to, and within, such areas of marked fibrosis were not completely occluded. Such areas are often quite irregular in outline, and the fibrosis within them has a very patchy distribution. They represent, in some instances, a coalescence of several small areas of fibrosis, such as those which are observed after a single experimental production of temporary ischemia in the dog. The fact that such "infarcted areas" were found predominantly in the hearts of patients with angina pectoris is in accord with these considerations.

The Application of the Experimental Data Obtained in This Study to the Phenomenon of Cardiac Infarction in the Absence of Complete Occlusion of a Coronary Artery in man seems justifiable. As stated above, a sufficient species difference appears to exist between the myocardial blood supply of the cat and dog so that occlusions up to thirty-five minutes were not manifested by pathologic changes in the myocardiums of the cats, whereas occlusions of twenty-five minutes and more caused these changes in dogs. The mechanism whereby massive myocardial infarction is produced by temporary interruption of the blood supply to a part of the dog's heart for forty or more minutes is analogous to that of the occurrence of myocardial infarction without coronary occlusion in man. Myocardial necrosis in man may occur (1) after sudden occlusion of a previously adequate arterial lumen, *before* a fully adequate anastomotic circulation has had an opportunity to develop or, (2) without fresh occlusion of any of the main coronary vessels or their larger branches, under circumstances, such as increased cardiac work, which predispose to prolonged myocardial anoxia. In the hearts of some patients, infarcts, old or fresh, have been found in the absence of any coronary occlusion (Blumgart, et al.,¹ Cases 8 and 28). In other hearts fresh occlusions may be present, but there are no old occlusions corresponding to the old healed infarcts, or fresh infarction may be disclosed without fresh coronary occlusion (Blumgart, et al.,³⁴ Case 3).

It is in accord with the experimental observations to consider that in a heart with multiple occlusions and narrowings, and thus with an anastomotic but reduced blood supply, slight further narrowing of several blood vessels by any one of several mechanisms, or increased demands on the myocardium because of rapid ventricular rates, effort, etc., may produce a large area of ischemia. This ischemic area may then undergo necrosis, with the production of a large infarct. In several of the cases previously studied, infarction was undoubtedly favored by the fact that these patients did not rest after the onset of occlusion, but continued to work or persist in other activity, thereby increasing the degree and duration of ischemia.

SUMMARY

1. Experiments were performed on thirty-nine dogs to learn whether temporary occlusion of a coronary artery would produce myocardial infarction and persistent electrocardiographic changes characteristic of myocardial ischemia.

2. In twelve of eighteen animals which were allowed to survive four or more days, electrocardiographic changes typical of myocardial ischemia, and of a character not observed in control experiments, were found during the first few days to weeks after occlusion of a coronary artery for five to forty-five minutes. The type, anterior or posterior, of these electrocardiographic changes varied according to whether the anterior descending or left circumflex artery was temporarily occluded.

3. Eight animals died of ventricular fibrillation during the first five minutes of occlusion of the artery, or on re-establishment of the circulation after occlusions lasting fifteen to thirty minutes.

4. No gross evidences of myocardial infarction were found in the seven animals which lived for four to forty days after occlusion of a coronary artery had been maintained for five to twenty minutes.

5. There were gross evidences, proved subsequently by microscopic examination, of infarction in eight of eleven experiments in which occlusion of a coronary artery was maintained for twenty-five to forty-five minutes.

6. In the hearts which showed infarction, the extent of the infarct was roughly in direct proportion to the duration of the arterial occlusion; the infarcted area in several of the hearts in which an artery had been occluded for forty to forty-five minutes was as large as that which occurs after permanent and complete occlusion of the artery.

7. These observations afford evidence that temporary ischemia may cause irreversible myocardial changes, and, if the ischemia be of sufficient duration, may cause myocardial infarction of the same character and degree as that which occurs after permanent and complete occlusion of an artery.

8. The electrocardiographic and myocardial observations on certain patients with coronary artery disease are discussed with reference to the information gained in this study.

We wish to thank Dr. A. Baird Hastings for generously providing facilities which made these studies possible.

REFERENCES

1. Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Studies on the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis, and Myocardial Infarction to the Pathologic Findings, With Particular Reference to the Significance of the Collateral Circulation, *AM. HEART J.* 19: 1, 1940.
2. Bean, W. B.: Infarction of the Heart. III. Clinical Course and Morphological Findings, *Ann. Int. Med.* 12: 71, 1938.
3. Friedberg, C. K., and Horn, H.: Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, *J. A. M. A.* 112: 1675, 1939.

4. Gross, H., and Sternberg, W. H.: Myocardial Infarction Without Significant Lesions of Coronary Arteries, *Arch. Int. Med.* 64: 249, 1939.
5. Blumgart, H. L., Hoff, H. E., Landowne, M., and Schlesinger, M. J.: Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries in Producing Persistent Electrocardiographic Changes, *Am. J. M. Sc.* 194: 493, 1937.
6. Wolff, H. G.: The Cerebral Circulation, *Physiol. Rev.* 16: 545, 1936.
7. Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, *Arch. Neurol. & Psychiat.* 23: 876, 1930.
8. The Circulation of the Brain and Spinal Cord. A Symposium on Blood Supply. Proc. Association for Research in Nervous and Mental Diseases, New York, Dec. 27 and 28, 1937. Baltimore, 1938, Williams & Wilkins Co.
9. Barnes, A. R., and Mann, F. C.: Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, *AM. HEART J.* 7: 477, 1932.
10. Harris, B. R., and Hussey, R.: The Electrocardiographic Changes Following Coronary Artery Ligation in Dogs, *AM. HEART J.* 12: 724, 1936.
11. Mallory, G. K., White, P. D., and Salcedo-Salgar, J.: The Speed of Healing of Myocardial Infarction. A Study of the Pathologic Anatomy in Seventy-Two Cases, *AM. HEART J.* 18: 647, 1939.
12. Blumgart, H. L., Hoff, H., Landowne, M., and Schlesinger, M. J.: Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries, *Tr. A. Am. Physicians* 52: 210, 1937.
13. Tennant, R., Grayzel, D. M., Sutherland, F. A., and Stringer, S. W.: Studies on Experimental Coronary Occlusion; Chemical and Anatomical Changes in the Myocardium After Coronary Ligation, *AM. HEART J.* 12: 168, 1936.
14. Tennant, R.: Studies in Pathology of Vascular Disease; Studies on Experimental Coronary Occlusion, *Yale J. Biol. & Med.* 9: 60, 1936.
15. Fauteux, M.: A New Surgical Method to Improve the Blood Supply to the Heart in Coronary Disease. Reported to Harvard Medical Society Meeting of October 10, 1939. *New England J. Med.* 221: 915, 1939.
16. Bronson, L. H.: Anatomical and Chemical Changes in the Myocardium Following Short-Term Coronary Artery Occlusion in Dogs, *Yale J. Biol. & Med.* 10: 405, 1938.
17. Hastings, A. B., Blumgart, H. L., Lowry, O. H., and Gilligan, D. R.: Chemical Changes in the Heart Following Experimental Temporary Coronary Occlusion, *Tr. A. Am. Physicians* 54: 237, 1939.
18. Lowry, O. H., and Gilligan, D. R.: Chemical Changes in the Myocardium of Dogs Following Experimental Temporary Coronary Artery Occlusion. (In preparation.)
19. Tureen, L. L.: Effect of Experimental Temporary Vascular Occlusion on the Spinal Cord. I. Correlation Between Structural and Functional Changes, *Arch. Neurol. & Psychiat.* 35: 789, 1936.
20. Heymans, C., Jourdan, F., and Nowak, S. J. G.: Recherches sur la résistance des centres encephalo-bulbaires à l'anémie, *Compt. rend. Soc. de biol.* 117: 470, 1934.
21. Heymans, C., and Bouckaert, J. J.: Sur la survie et la réanimation des centres nerveux, *Compt. rend. Soc. de biol.* 119: 324, 1935.
22. Simpson, H. N., and Derbyshire, A. J.: Electrical Activity of the Motor Cortex During Cerebral Anemia, *Proc. Am. Physiol. Soc. Am. J. Physiol.* 109: 99, 1934.
23. Kabat, H., and Dennis, C.: Decerebration in the Dog by Complete Temporary Anemia of the Brain, *Proc. Soc. Exper. Biol. & Med.* 38: 864, 1938.
24. Cannon, W. B., and Burket, I. R.: The Endurance of Anemia by Nerve Cells in the Myenteric Plexus, *Am. J. Physiol.* 32: 347, 1913.
25. Tureen, L. L.: Effect of Experimental Temporary Vascular Occlusion on the Spinal Cord. II. Changes in Mineral Salt Content of Nerve Cells, *Arch. Neurol. & Psychiat.* 39: 455, 1938.
26. Pianetto, M. B.: The Coronary Arteries of the Dog, *AM. HEART J.* 18: 403, 1939.
27. Unpublished observations.
28. Rothschild, M. A., and Kissin, M.: Production of the Anginal Syndrome by Induced General Anoxemia, *AM. HEART J.* 8: 729, 1933.
29. Wood, F. C., and Wolferth, C. C.: Angina Pectoris. The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison With the Effects of Experimental Temporary Coronary Occlusion, *Arch. Int. Med.* 47: 339, 1931.

30. Riseman, J. E. F., and Brown, M. G.: The Sedimentation Rate in Angina Pectoris and Coronary Thrombosis, *Am. J. M. Sc.* 194: 392, 1937.
31. Saphir, O., Priest, W. S., Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis, and the Resulting Myocardial Changes. An Evaluation of Their Respective Clinical Pictures Including the Electrocardiographic Records, Based on the Anatomical Findings, *AM. HEART J.* 10: 567, 1935.
32. Büchner, F., Weber, A., and Haager, B.: *Koronarinfarkt und Koronarinsuffizienz*, Leipzig, 1935, Georg Thieme.
33. Schlesinger, M. J.: An Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, *AM. HEART J.* 15: 528, 1938.
34. Blumgart, H. L., Schlesinger, M. J., and Zoll, P. M.: Angina Pectoris, Coronary Failure and Acute Myocardial Infarction. The Role of Coronary Occlusions and Collateral Circulation, *J. A. M. A.* 116: 91, 1941.

FETAL ELECTROCARDIOGRAPHY

HUBERT MANN, M.D., AND PHINEAS BERNSTEIN, M.D.
NEW YORK, N. Y.

THE scope of practical electrocardiography can be extended to cover a considerable period of intrauterine life. Heretofore, workers in this field have obtained satisfactory tracings during the eighth and ninth months of pregnancy. The modified technique developed by e of us on (H. M.) consistently yields reliable records from the sixth month of pregnancy to term, and even before the sixth month we have occasionally secured tracings. The application of this technique to a group of forty unselected obstetrical patients and the results obtained form the basis of this report.

HISTORY

The development of the string galvanometer and its successful application in recording the action current of the heart in adults and children led naturally to attempts to obtain fetal electrocardiograms. As early as 1906, Cremer¹ recorded and published fetal electrocardiograms which were taken during the last month of pregnancy. He used two electrodes, one placed in the vagina and one on the abdomen, and his published curves show distinct fetal deflections. This single, early success, however, did not result in any further progress. Attempts to develop a standard method of fetal electrocardiography were unsuccessful because of technical difficulties. The fetal heart was not only small, and, therefore, presumably generated smaller action currents, but it was also separated from the outside by amniotic fluid, fetal membranes, uterus, maternal viscera, and abdominal wall. The application of the electrodes, which presented little difficulty in ordinary electrocardiography, was another problem. Sachs,² in 1922, tried to record the electrocardiogram of the fetus in utero by means of abdominovaginal and abdominorectal leads, but he failed to obtain any deflections which could be identified definitely as fetal in origin.

The invention of the audion tube, with the subsequent rapid development of electrical amplifiers, suggested the use of an amplifier to increase the sensitivity of the string galvanometer. Such an amplifier, when properly designed, presented several distinct advantages over the use of the string galvanometer alone. It greatly increased the sensitivity of the instrument and permitted the recording of smaller currents than could be registered with the string galvanometer alone. It simplified the

problem of skin resistance and permitted the use of smaller electrodes. It eliminated the technical problem of compensating for skin currents, and prevented wandering of the string. By means of such a combination of valve amplifier and string galvanometer, Mackawa and Toyoshima³ succeeded, in 1930, in recording the action current of the heart of a full-term fetus in utero several hours before birth. They placed the electrodes on the abdomen, and obtained a curve which showed not only the mother's electrocardiogram, but also an independent deflection which corresponded in rate to the fetal heart rate, and which, in the light of later work, notably by Bell,⁴ was definitely a fetal electrocardiogram.

The combination of amplifier and string galvanometer, although it had numerous advantages, was cumbersome, difficult to manipulate, and subject to much outside electrical and mechanical interference. Improvements in the string galvanometer and in technique enabled Steffan and Strassmann⁵ to obtain a fetal electrocardiogram with this instrument alone, in 1933. In 1938, Strassmann and Mussey⁶ reported a series of fifty-two patients who were examined during the last seventy days of pregnancy. Of the seventy electrocardiograms which were taken, sixty-one, or 87 per cent, showed a fetal electrocardiogram, and nine, or 13 per cent, failed to show any discernible fetal curve.

Easby,⁷ in 1934, succeeded in obtaining an electrocardiogram of a 4.5-month-old fetus which had been removed from the uterus after hysterectomy, and Heard, Burkley, and Schaefer,⁸ in 1936, reported eleven electrocardiograms of fetuses which had been removed from the uterus either by operation or by spontaneous delivery. These curves are valuable and interesting, but have little bearing on the subject of routine, antenatal, fetal electrocardiography.

Johnson,⁹ in 1938, published a standard electrocardiogram of a primipara who was almost at term in which fetal deflections were observed and identified. The instrument which he used was of the standard amplifier type, and the recording of the fetal deflections was not intentional. However, the fact that fetal deflections could be observed in an ordinary electrocardiogram, taken in the usual way, suggested that it might be possible to obtain fetal electrocardiograms routinely by a refinement of the technique. The amplifier electrocardiograph had now succeeded in eliminating much of the outside electrical and mechanical interference which had been so disturbing to early workers. In addition, the instrument was portable, and therefore could be carried to the bedside. Furthermore, its standard sensitivity could be doubled by a mere turn of a knob. A preliminary test on several patients indicated that the development of a routine method for fetal electrocardiography was possible.

The technique devised by Mann was standardized as follows. The patient reclines on her back in bed, or on a comfortable couch. Standard electrodes are applied to the arms, near the shoulders, and to the upper part of the left leg. The ordinary three

leads of the electrocardiogram are taken with the amplifier adjusted to give a deflection of 2 cm. per millivolt, or twice the usual deflection. Twenty-five or more beats are recorded in each lead. The electrode on the left leg is then transferred to the upper part of the right leg, and three leads are again taken. Lead I is, of course, the same as the first Lead I. The electrodes are now removed from the arms and leg, and two electrodes are placed on the abdomen in the following six positions: (1) Right upper quadrant, symphysis pubis; (2) epigastrium, symphysis; (3) left upper quadrant, symphysis; (4) right upper quadrant, left upper quadrant; (5) right umbilical region, left umbilical region; (6) right lower quadrant, left lower quadrant.

The right arm wire is attached to the first electrode, and the left arm wire to the second electrode; the lead selector is placed on Lead I, and double amplification is used, as before. Six strips of twenty-five beats each are taken. The first three represent, respectively, the right, central, and left oblique diameters of the abdomen, and the last three are transverse. There is no difficulty in applying abdominal electrodes. A bit of electrode paste is rubbed on the skin. The electrode is applied, covered with a towel, and held in place by the patient's hand, which rests lightly on the towel.

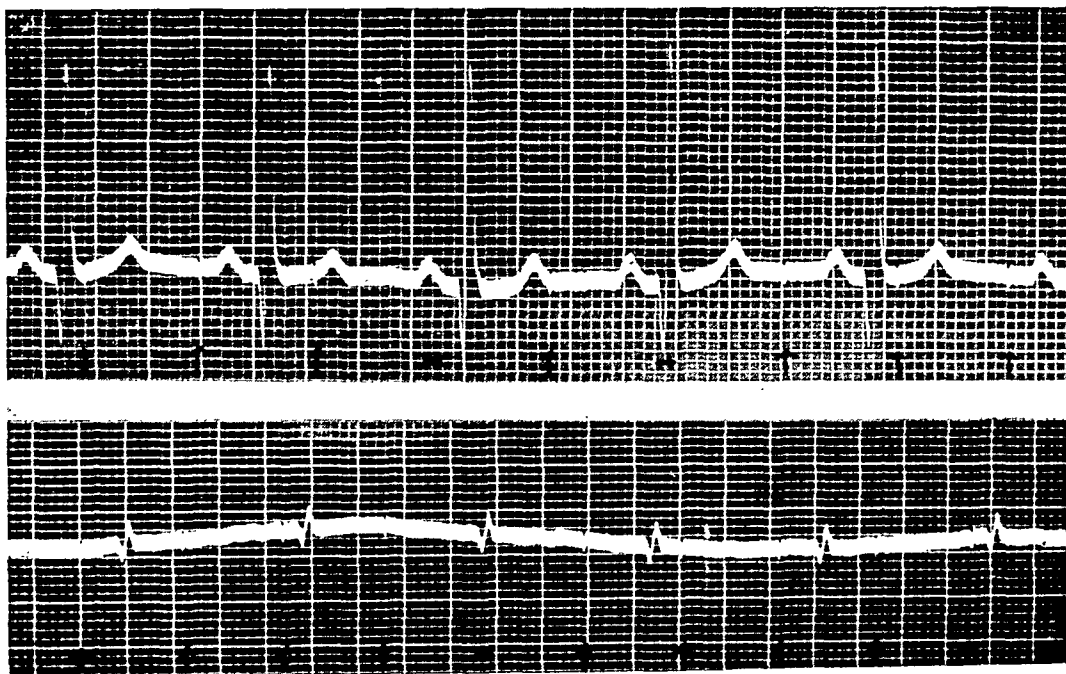


Fig. 1.—Fetal electrocardiograms taken two days before delivery. The upper curve was made with electrodes on the left arm and right leg. The lower curve was taken with electrodes on the abdomen. Standardization of both curves is 2 cm. per millivolt. The arrows indicate fetal deflections.

It will be noted that in this way both limb leads and abdominal leads are taken; this permits a comparison of the value of the two types of external leads which have been advocated for fetal electrocardiography. This comparison is shown in detail later. In general, it may be said that the fetal electrocardiogram, as shown in the abdominal leads, is easier to identify and more suitable for study. The maternal deflections are much smaller in the abdominal leads; the abdominal muscles rarely exhibit tremor, and the fetal deflections are larger than in the limb leads.

The fetal electrocardiogram does not appear equally clearly in all the abdominal leads, but shows considerable variation which is caused probably by changes in the axis of the fetus and anatomic variations in the abdominal organs of the mother. The maternal deflections in the limb leads frequently obscure the much smaller fetal deflections, and, at times, it is very difficult to eliminate small muscle tremors in the limbs.

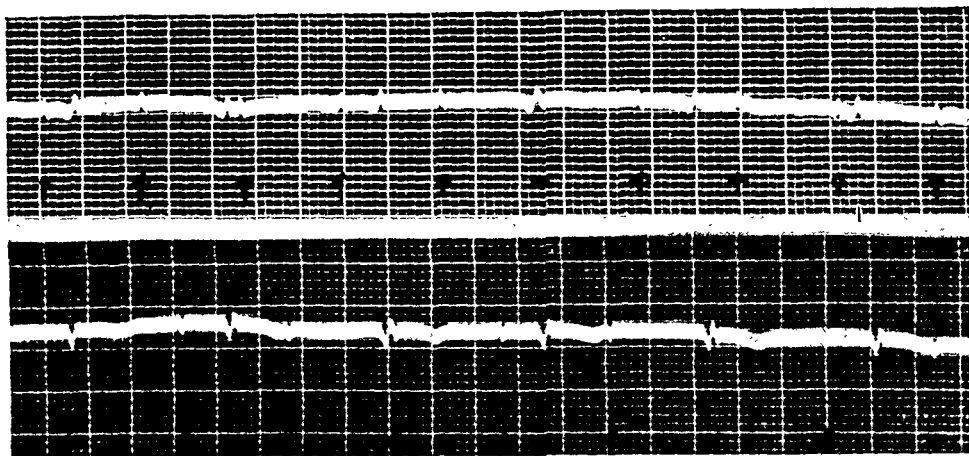


Fig. 2.—Fetal electrocardiogram taken four days before delivery. Two abdominal leads are shown. Arrows indicate fetal deflections.

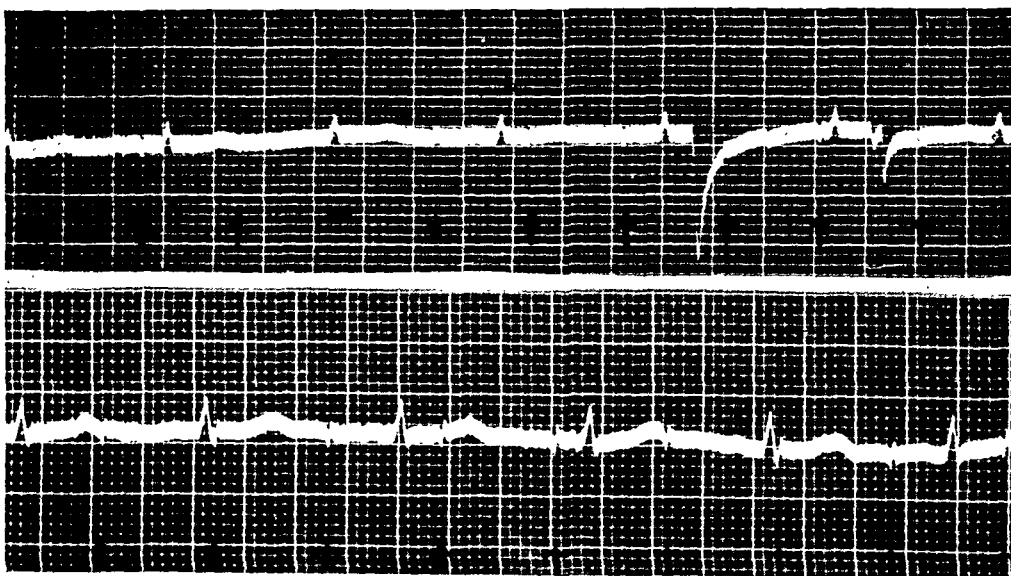


Fig. 3.—Fetal electrocardiograms recorded with abdominal electrodes. The upper curve was taken 128 days before delivery, and the lower curve, 111 days before delivery. The arrows indicate fetal deflections.

Fig. 1 shows a fetal electrocardiogram which was taken in the last month of pregnancy. The upper curve was recorded with electrodes on the left arm and right leg. The lower curve was recorded with one electrode on the epigastrium and the other at the symphysis. The standardization in both curves was the same, namely, 2 cm. per millivolt. It will be noted that, although the fetal deflections are about the same size

in the two curves, they are more easily identified in the lower curve because the maternal waves are much smaller in the abdominal lead.

Fig. 2 shows a fetal electrocardiogram which was taken four days before delivery. Two abdominal leads are shown. The maternal waves are small, and the fetal deflections are readily identified.

The use of abdominal leads permits identification of fetal waves as early as the fifth month of pregnancy. Fig. 3 shows two curves which were taken with the electrodes placed to the right and left of the umbilicus, and recorded 128 and 111 days, respectively, before birth of normal, full-term children.

In exceptional cases, fetal waves have been recorded by us as early as the end of the fourth month of gestation, but the fetal curve is most readily observed during the last 100 days of pregnancy. This is shown in Table I, which is a complete list of our attempts to record fetal electrocardiograms on the forty patients of this series.

The plus and minus signs indicate the presence or absence of a detectable fetal curve. Only those curves in which the fetal deflection could be counted, for at least thirty beats, were considered positive. Doubtful curves were regarded as negative. The numbers indicate the time, in days before delivery, at which the electrocardiograms were taken.

It will be noted that all curves which were taken more than 169 days before delivery failed to show fetal waves and that the proportion of negative curves decreased sharply after the one hundred fiftieth day, so that, by the third month before delivery, many positive curves had appeared. During the last three months of pregnancy, positive curves were the rule, and negative curves, the exception; of the forty patients in our group, thirty-six showed positive fetal electrocardiograms. Of the four patients on whom no fetal curve was recorded, three had electrocardiograms only once, on the one hundred fifty-eighth, one hundred fifty-fourth, and one hundred thirty-seventh days, respectively, before delivery, and the other had two electrocardiograms, on the one hundred seventy-fifth and ninety-sixth days, respectively, before delivery.

A comparison of limb leads and abdominal leads is interesting. Of the thirty-six patients who showed fetal electrocardiograms, twelve had positive curves in the limb leads, and the total number of limb leads in which the fetal electrocardiogram could be identified was twenty-six. Of this same group, thirty-four had positive curves in the abdominal leads, and the total number of abdominal leads in which the fetal electrocardiogram could be identified was 150. Two patients had positive curves only in the limb leads, and twenty-four had positive curves only in the abdominal leads. Ten patients showed positive curves in both limb and abdominal leads. In general, the abdominal leads were definitely superior, both with respect to the number of positive curves, and the ease with which the fetal curve could be identified.

TABLE I
FETAL ELECTROCARDIOGRAMS

CASE NO.	DAYS BEFORE DELIVERY			
1	+20			
2	+6	+41		
3		+51		
4	+24	+52		
5	+31	+59		
6		+68		
7	+26			
8		+46	+83	
9		+41	-83	
10			-78	+107
11			+90	+111
12			+86	-127
13		+43		+128
14*				+147 -168
15	+21			-153 -175
16			-96	-175
17	+30			-150
18	+32			-146
19				+148 -201
20				+144 -200
21	+4	+26		-110
22*			+109	
23				-158
24	+1 $\frac{1}{3}$			
25	+26	+47		+157
26		+38		+126
27	+21		+74	-137
28		+31		+131
29	+7	+47		+139
30	+16	+51		-162
31	+23		-74	+137
32			+89	+165
33		+39	+107	+169
34				+133
35		+39	+111	
36			+117	-181
37				-137
38				-154
39			+120	
40*			+78	

+ indicates that fetal electrocardiogram is present.

- indicates that fetal electrocardiogram is absent.

In forty cases there are fifty-six positive and twenty negative fetal electrocardiograms.

*Delivery premature, calculation approximate.

The relationship between fetal heart rate and sex can be investigated statistically by means of the electrocardiogram. Counts of at least thirty fetal beats gave us the heart rates of those babies in our series whose sex is now known. Stillborn, premature, and abnormal children were excluded. A total of forty-three counts was made in the last five months of pregnancy. Twenty-one of these counts were made on thirteen male fetuses. Twenty-two counts were made on sixteen female fetuses. The rates of the females averaged about 144 beats per minute, and those of the males, about 141 per minute. This difference is insignificant, particularly in such a small series.

TABLE II
FETAL HEART RATES

MALE	FEMALE
138*	124
154	137
137*	151
134	140
142	147*
136	151
144	152*
140	147
134*	154
149*	138
136*	137†
155†	149*
135	158*
	138
	150
	137
Av. 141	144

*Average of two counts.

†Average of three counts.

Fetal electrocardiography may suggest the presence of certain abnormalities in utero, and, for this reason alone, the procedure warrants further study and use whenever unusual conditions are suspected. Not all abnormalities, however, are demonstrable by this means. The results obtained in the following unusual and anomalous conditions are of interest.

In one case¹⁰ of hydramnios and ectopia intestinalis fetalis (gastro-schisis), electrocardiograms were made forty-two days and six days before delivery. In both tracings the fetal heart rate was abnormally rapid, and was much faster the second time than the first, thirty-six days earlier. Although the rapid rates suggested fetal distress, the actual condition could not be diagnosed clinically.

A premature, living baby which was delivered in the seventh month of pregnancy showed no abnormalities of the heart rate in a tracing taken forty-nine days before delivery. Birth weight was 3 pounds, 13 ounces.

TABLE III
FETAL AND MATERNAL HEART RATES AT DIFFERENT PERIODS BEFORE DELIVERY

RATE	DAYS BEFORE DELIVERY																
	0	10	20	30	40	50	60	70	80	90	100	110	120	130	140	150	160
	TO 9	TO 19	TO 29	TO 39	TO 49	TO 59	TO 69	TO 79	TO 89	TO 99	TO 109	TO 119	TO 129	TO 139	TO 149	TO 159	TO 169
Fetal	131		124	144	134	137	140	143	140	148	142	146	158	150	147	162	149
Maternal	89		78	79	78	80	105	76	63	81	94	73	92	83	108	84	75
Fetal	138		139	140	134	136		151	151		151	138	152	138	154		171
Maternal	89		111	93	93	89		87	87		89	86	92	85	94		75
Fetal			154	147	146	151		167	167			150	137				
Maternal			106	95	88	71		78	78			75	69				
Fetal			136	148	124												
Maternal			64	98	95												
Fetal			137	144													
Maternal			90	86													
Fetal			125	132													
Maternal			94	77													
Fetal			129														
Maternal			71														
Fetal (Av.)	135		135	143	135	141	140	143	153	148	147	145	149	144	151	162	160
Maternal (Av.)	89		88	88	89	80	105	76	76	81	92	78	84	84	101	84	75

A premature, stillborn infant which was delivered in the eighth month of pregnancy had a normal heart rate fifty-seven days before delivery. Birth weight was 4 pounds.

In a recent case in which the obstetrician was uncertain as to whether or not the child was alive, an electrocardiogram failed to reveal fetal deflections. Two days later, an 8-month-old, macerated fetus was delivered.

One patient had twins; the first to be born was a male which occupied the right occipitoanterior position, and the other, a female, lay transversely in the fundus. Electrocardiograms which were taken sixteen and fifty-one days before term revealed an excellent record of but *one* fetus. Re-examination of the curves failed to reveal a second fetal electrocardiogram.

The electrocardiogram of a full-term baby which died twelve hours after birth from multiple heart lesions (autopsy confirmation) was normal twenty-three days and 137 days before delivery. The anomalies consisted of patent foramen ovale, absent interventricular septum, single arterial trunk (aorta), with pulmonary arterial branches, hypoplasia of the mitral valve, and opening of a rudimentary mitral orifice into the right ventricle. Re-examination of the fetal electrocardiogram failed to disclose any abnormality.

The relation of the fetal heart rate to the age of the fetus, as well as to the maternal heart rate, is subject to exact study by this method. Table III shows the fetal and maternal heart rates in our cases during the last five months of pregnancy. The rates were calculated by counting the number of beats recorded in twelve to twenty seconds of continuous recording. There did not seem to be any constant or obvious relation between the fetal and the maternal heart rate, but there was a slight tendency for the fetal rate to be more rapid early in pregnancy.

In counting the fetal heart rate it is often possible to observe temporary changes in rate corresponding to the sinus arrhythmia of adults. We observed changes in the fetal rate during periods of relative anoxemia caused by paroxysmal tachycardia in the mother. The effect of administering drugs to the mother, and of tobacco smoking, may be studied by this method.

The relationship between the position of the fetus and the character of the fetal electrocardiogram is of interest. Until the last month of pregnancy the fetal position is not fixed, so that attempts to ascertain the position by the contour of the electrocardiogram have little practical value. During the final month of pregnancy the fetal presentation is generally determined, and can be readily ascertained by the commonly used obstetrical methods. With the usual vertex presentation, the direction and shape of the fetal deflections correspond to what we expect to find, bearing in mind the positions of the electrodes and the fact that

the fetus is inverted. The fetal deflection is generally diphasic, but because of its small size few details can be observed. During the latter part of our investigation, the laboratory which manufactures the electrocardiograph which we employed submitted for experimental use an instrument with increased amplifying power. With this new instrument an amplification of about 5 cm. per millivolt was readily obtained. With such amplification it should be possible to study more closely the shape of the fetal ventricular complex.

SUMMARY AND CONCLUSIONS

1. A modified technique of fetal electrocardiography is presented, with illustrative curves. Abdominal leads were found to be superior to limb leads.

2. The history of fetal electrocardiography is briefly sketched.

3. The method has limitations and shortcomings which are still to be eliminated.

4. Of significance was the large number of satisfactory tracings which were obtained during the last trimester of pregnancy, namely, 90 per cent, or thirty-six of forty curves. The earliest clearly defined curve was obtained on the one hundred sixty-ninth day before term (during the fourth month of gestation). As far as we are aware, no fetal electrocardiogram has ever been obtained earlier than this.

5. In some cases, fetal distress or death in utero can be definitely diagnosed.

6. Fetal anomalies and congenital heart disease, per se, do not reveal themselves electrocardiographically.

7. From the observations so far, sex cannot be prognosticated. Conclusions from a larger study will soon be forthcoming.

8. There is no obvious relationship between the fetal and maternal heart rates. Fetal rates are generally more rapid early in pregnancy.

9. The relationship between the fetal position in utero and the size and shape of the electrocardiographic deflections, fetal arrhythmias, and drug effects on fetal rate can be studied accurately by this method.

10. The effects of maternal anoxemia, as well as sinus arrhythmia, upon the fetal rate have been observed.

11. The diagnostic possibilities of the technique described should be investigated further.

REFERENCES

1. Cremer, Max: Ueber die direkte Ableitung der Aktionstroeme des menschlichen Herzens vom Oesophagus und ueber das Elektrokardiogramm des Foetus, München. med. Wchnschr. 17: 811, 1906.
2. Sachs, H.: Elektrokardiogrammstudien am Foetus in Utero, Pfüger's Arch. f. d. ges. Physiol. 197: 536, 1922.
3. Maekawa, M., and Toyoshima, J.: The Fetal Electrocardiogram of the Human Subject, Acta scholae med. univ. imp. in Kioto 12: 519, 1930.
4. Bell, G. H.: The Human Foetal Electrocardiogram, J. Obst. & Gynaec. Brit. Emp. 45: 802, 1938.

5. Steffan, H., and Strassmann, E. O.: Das fetale Elektrokardiogramm, Zentralbl. f. Gynäk. 57: 610, 1933.
6. Strassmann, E. O., and Mussey, R. D.: Technic and Results of Routine Fetal Electrocardiography During Pregnancy, Am. J. Obst. & Gynec. 36: 986, 1938.
7. Easby, M. H.: Electrocardiograms From a Four and a Half Months Old Fetus, AM. HEART J. 10: 118, 1934.
8. Heard, J. D., Burkley, G. G., and Schaefer, C. R.: Electrocardiograms Derived From Eleven Fetuses Through the Medium of Direct Leads, AM. HEART J. 11: 41, 1936.
9. Johnson, A. S.: An Unexpected Electrocardiogram of the Fetus, J. A. M. A. 111: 916, 1938.
10. Bernstein, P.: Gastroschisis, a Rare Teratological Condition in the Newborn, Arch. Pediat. 57: 505, 1940.

1150 FIFTH AVENUE
1100 PARK AVENUE

THE WOLFF-PARKINSON-WHITE SYNDROME, WITH PAROXYSMS OF VENTRICULAR TACHYCARDIA

SAMUEL A. LEVINE, M.D., AND PAUL B. BEESON, M.D.
BOSTON, MASS.

A PECULIAR syndrome was first described by Wolff, Parkinson, and White¹; it consists of a short P-R interval and bundle branch block in the electrocardiogram, and it occurs in patients who have paroxysms of tachycardia, but are otherwise apparently well. There have since been other reports of similar cases, in all of which there is a fairly uniform pattern. Although isolated cases of a somewhat similar type were previously reported by Wilson,² Wedd,³ and Hamburger,⁴ it was not until the publication by Wolff, et al., that the condition was really called to the attention of the medical profession. The syndrome is unique, and therefore deserves to be regarded as a clinical entity. For the present, because of the difficulty in describing the condition in a simple expression, it might be termed the "Wolff-Parkinson-White Syndrome." When it was first described, it was pointed out that these patients have attacks of tachycardia, for the most part of auricular origin, and, less frequently, paroxysmal auricular fibrillation. One peculiarity was that, while the heart was beating slowly and normally, the P-R time was short (0.08 to 0.10 second) and the QRS interval was markedly increased (0.10 to 0.12 second), whereas, during paroxysms, when the rate was rapid, the QRS interval was normal. It was also noted that these patients showed spontaneous reversion to normal P-R and QRS intervals without an attack of tachycardia or as a result of atropine administration. It is of interest that in the majority of the previously reported cases the patients were males; this sex discrepancy also prevails in ordinary, benign, paroxysmal auricular fibrillation.⁵

The mechanism of this abnormality is by no means clear; various hypotheses have been suggested. The appearance of the ventricular complexes is like that of bundle branch block, and the short P-R interval makes one wonder whether the pacemaker is in the A-V junctional tissue. Wolferth and Wood⁶ discussed the possibility that the impulse may reach the ventricles from the auricles through an abnormal pathway, the so-called bundle of Kent. It is not the purpose of this paper to discuss theories concerning the mechanism involved, but rather to report three additional cases in which there were unusual features.

From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, and the Department of Medicine, Harvard Medical School.

Received for publication Jan. 13, 1941.

In practically all of the previously reported instances of this syndrome, when the paroxysms were identified, they were found to be auricular in origin, i.e., either tachycardia or fibrillation, but our three patients had paroxysms of *ventricular* tachycardia. Only two such cases have so far been reported.^{7, 8} As will be seen below, these attacks occurred in patients who had no other evidence of organic heart disease; they all showed characteristic electrocardiograms when the heart rate was slow and curves typical of ventricular tachycardia when the rate was rapid. In order to emphasize some practical and clinical aspects of this condition that may not be fully appreciated, a fourth case, in which the paroxysms were of auricular rather than ventricular origin, is discussed.

CASE 1.—S. G., (Med. No. 55244), a 13-year-old white boy, was admitted to the Medical Service of the Peter Bent Brigham Hospital in the evening of June 6, 1939, complaining of pain in the chest and shortness of breath of seven hours' duration. He had had whooping cough and mumps at an early age and measles at 10. There was no other history of infections. His growth and development had been entirely normal. On the day of admission he had played as usual, and felt perfectly well until 7:00 P.M., when, while standing quietly, he suddenly felt weak and breathless. He gradually developed an aching pain beneath the sternum, and vomited. He was put to bed. The patient stated that he "felt as if his heart was pounding all over his body." A physician who was called attempted to stop the attack by carotid sinus pressure. This gave no relief, so that a hypodermic injection was administered, and he was brought to the hospital 4½ hours after the onset.

On admission to the hospital his temperature was 98.6° F.; his pulse was weak, thready, and irregular, and the rate at the wrist was about 80 per minute. The respiratory rate was 30 per minute. The blood pressure readings were unsatisfactory; some beats were audible at 95 mm. Hg, and others were heard down to 80 mm. Hg, but none below that level. The patient was a well-developed and well-nourished boy who appeared to be somewhat more than 13 years of age. He insisted on sitting upright, gasped for air, and complained of pain beneath the sternum. The lips and nail beds were cyanotic; the skin was pale, cool, and moist. The neck veins were not distended. Examination of the heart showed that the apex impulse was rather forceful and diffuse, and lay 9 cm. from the midsternal line. No thrills were felt, and there was no cardiac dullness to the right of the sternum. The heart sounds were described as follows: "The first sound at the apex was very loud, and the rate was extremely rapid. The rapid rate caused the heart to sound like the firing of a machine gun; a long period of regularity was followed by gross irregularities. The second sound was not remarkable, and no murmur was heard." The heart rate could not be counted accurately, but was said to be more than 200. The lungs were normal. The abdomen showed no tenderness or rigidity, and no mass was felt. The remainder of the physical examination revealed nothing remarkable. The leucocyte count was 9,000, and the urine was negative. The electrocardiogram showed ventricular tachycardia (Fig. 1). The patient was given morphine, which made him drowsy and more comfortable. He was also given 2.0 c.c. of digalen intramuscularly, without effect. Pressure on the eyeballs and on the carotid sinuses had no effect. He was then given 0.2 Gm. of quinidine sulfate orally. Forty minutes later his cardiac rate was found to have slowed to 80 per minute, and the rhythm was normal. An electrocardiogram at that time showed a short P-R interval and defective intraventricular conduction. The temperature rose to 99.6° F. by mouth on the second day.

There was no return of the tachycardia during the next seven days in the hospital. Since that time the patient has taken 0.2 Gm. of quinidine sulfate, daily, as a prophylactic measure, and has been seen from time to time. The electrocardiograms have shown little change. A roentgenogram at the time of his hospital admission, and another, one year later, showed no cardiac enlargement or abnormality in outline.

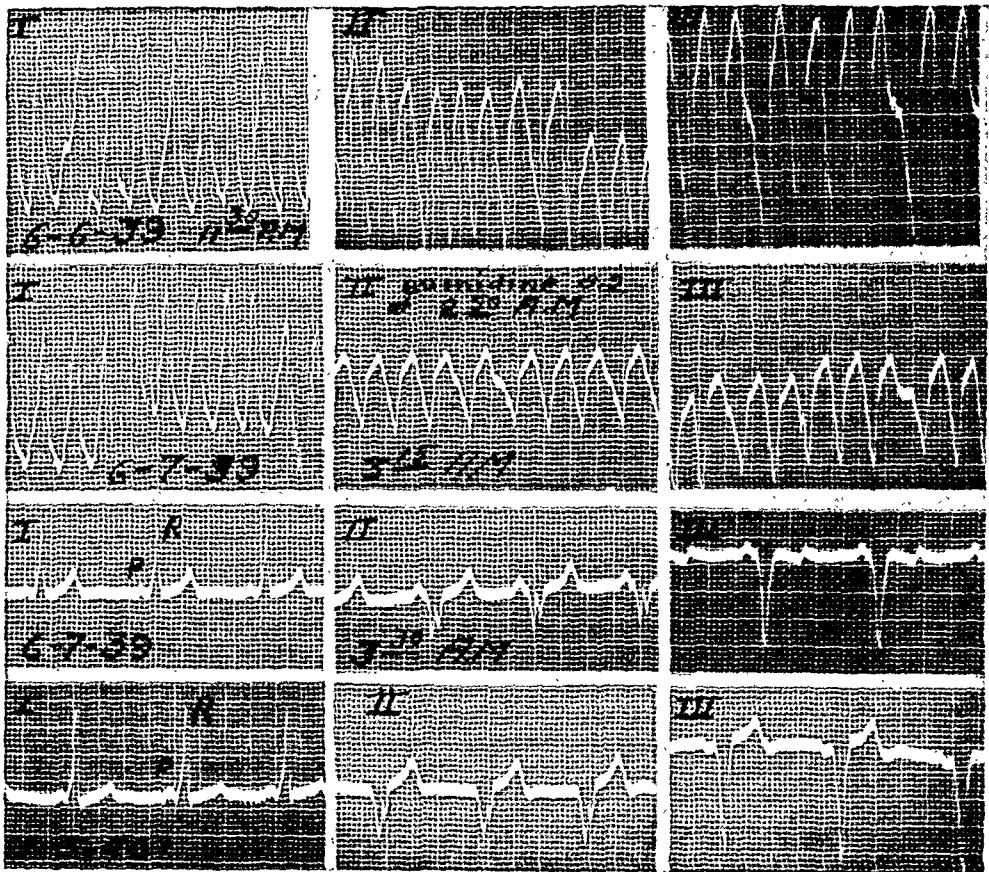


Fig. 1.—Case 1. First tracing shows ventricular tachycardia, with a rate of 292. Second tracing (twenty-five minutes after oral administration of 0.2 Gm. of quinidine) shows slowing of ventricular rate to about 225. Third set (forty minutes after administration of quinidine) shows slow normal rate. Note short P-R and long QRS intervals. Lowest set, taken seven months later, shows same mechanism.

Comment.—This patient had the typical electrocardiograms described by Wolff, et al., but the paroxysm of tachycardia was ventricular in origin. It is of importance that the attack, which was quite serious, was refractory to all the measures employed for paroxysms of auricular origin, but apparently responded promptly to quinidine. He has had no recurrence and has been taking quinidine regularly.

CASE 2.*—A 40-year-old white man, an office worker, was first seen in December, 1937. He complained of general malaise, headaches, insomnia, and a capricious appetite for the preceding six months. In addition, he had had a number of attacks of palpitation during that period of time. These attacks were not accompanied by

*We are greatly indebted to Dr. James B. McLester, of Birmingham, Ala., for giving us the data in this case.

pain or dyspnea, but he felt obliged to sit down and rest while they were present. They usually lasted about five minutes. Physical examination revealed no significant abnormalities. The heart was not enlarged; the sounds were normal; and there were no murmurs. The rhythm was normal and the rate was 90 per minute. The blood pressure was 100/60. A roentgenogram of the chest showed no cardiac enlargement and normal lung fields. Roentgenograms of the skull, sinuses, and gastrointestinal tract showed nothing abnormal. There was no anemia; the total and differential leucocyte counts were normal. The blood Wassermann reaction was negative. Urinalysis revealed nothing abnormal. There was free HCl in the gastric juice. The basal metabolic rate was normal. The electrocardiogram showed short P-R and prolonged QRS intervals, but otherwise was not remarkable.

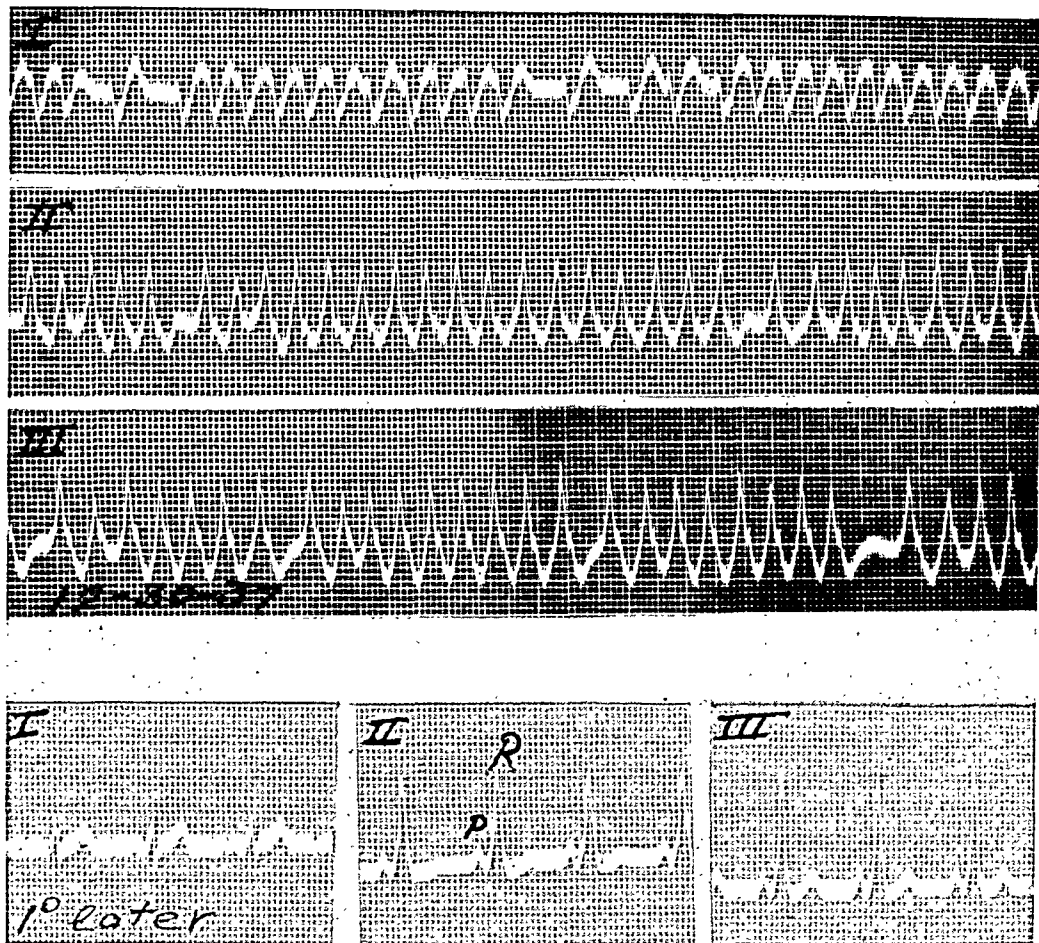


Fig. 2.—Case 2. Upper three leads show typical ventricular tachycardia; rate is 246. Lower set, one hour later, shows slow regular rate, with short P-R and prolonged QRS complexes.

Two days later the patient began to have palpitation in the evening, and the attack persisted until the next morning, when he returned to his physician's office. Examination showed that the heart rate was extremely rapid and could not be counted. At the wrist only 25 to 50 pulses per minute could be felt. The electrocardiogram which was taken at that time showed ventricular tachycardia (Fig. 2). One hour later the attack ceased spontaneously. Immediately after cessation of the attack another electrocardiogram was taken. This showed the same short P-R interval and prolonged QRS complex.

Unfortunately, this patient did not return for a follow-up examination, so that there is no information available as to his subsequent course.

Comment.—This case also belongs to the group with short P-R intervals and prolonged QRS complexes, but here again the paroxysm of tachycardia was of ventricular origin.

CASE 3.*—L. L. was a 36-year-old steamfitter who had always been in excellent health until the onset of an attack of tachycardia. This occurred at 8:30 A.M., Dec. 4, 1939. While lifting a heavy box, he suddenly became conscious of a "knock"

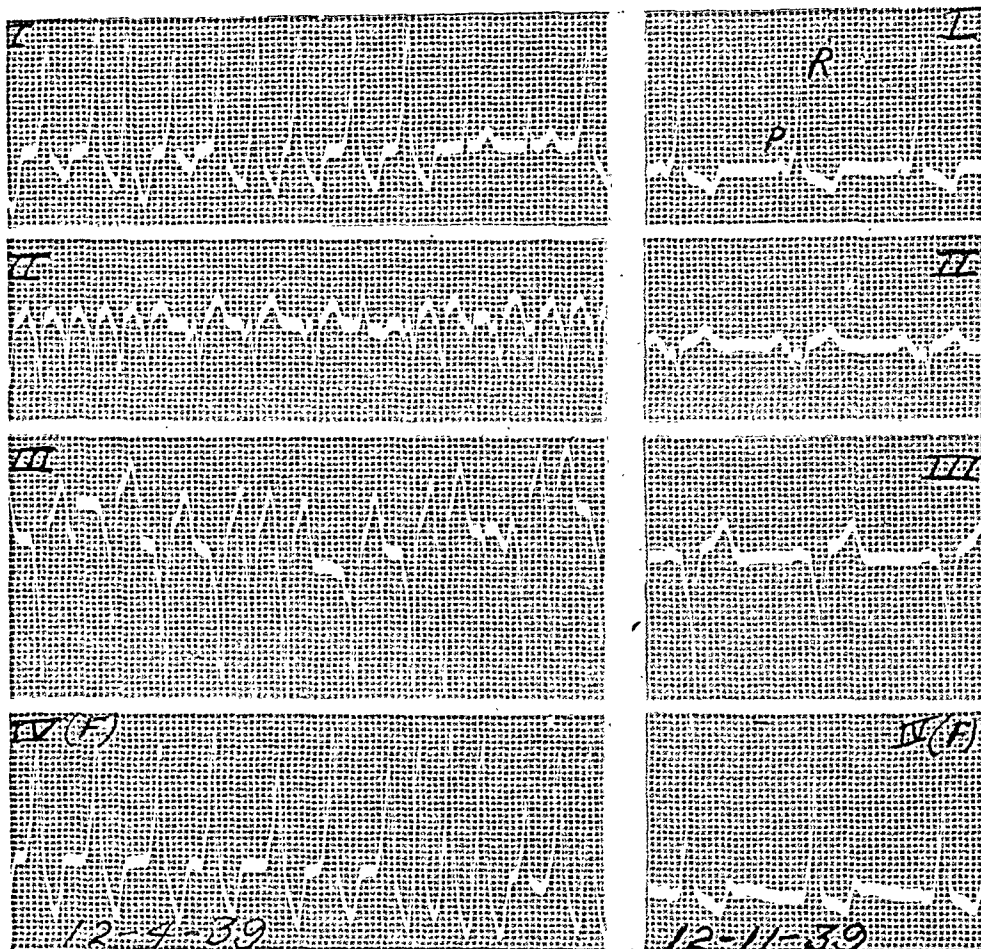


Fig. 3.—Case 3. Tracings on left show ventricular tachycardia, with occasional supraventricular beat; rate is 208. Set on the right shows slow regular rate, with short P-R and prolonged QRS intervals.

in the center of his chest, accompanied by dyspnea and extreme weakness; there was no real pain. He was transported to a hospital thirty miles away by automobile. On admission to the hospital he was found to be flushed but not dyspneic, and apparently in no great distress. The pulse rate was very rapid, and the heart-beat, totally irregular. The blood pressure was 115/75. The temperature was 99.2° F. (rectal). The electrocardiogram which was taken at that time showed ventricular tachycardia (Fig. 3). The tachycardia persisted until evening. At 11:00 P.M. he was given 0.8 Gm. of digitalis orally. At 2:00 A.M. the next day it was found that his heart rate had slowed to 96, with normal rhythm. Examination of the blood later that day showed no anemia; the leucocyte count was 14,700,

*We wish to thank Dr. T. F. Brewer of Hartford, Conn., for giving us some of the data in this case.

with 78 per cent polymorphonuclears. The electrocardiogram showed the characteristic, short P-R interval and bundle branch block (Fig. 3). The leucocyte count was 18,000 on the second hospital day, and during the remainder of his stay in the hospital it was 13,000 or 14,000. He was afebrile at all times. On December 8 a consultant examined him and noted that he was a thickset, muscular man who appeared perfectly well and had no complaints. The heart was not enlarged; the sounds were of good quality; the rhythm was normal; and the rate was 80 per minute. The blood pressure was 142/90. The lungs were normal. It was decided to treat the patient as if he had had a myocardial infarction; accordingly, he was kept in bed in the hospital for six weeks.

On Jan. 31 the patient was seen by one of us (S. A. L.). Physical and routine laboratory examinations showed nothing remarkable. The electrocardiogram was similar to the previous tracings. Roentgenologically, the lungs and heart were normal; the transverse diameter of the heart was 13.9 cm., and that of the chest was 29.8 cm. It was considered probable that the patient had not had infarction, and that all of the symptoms could be attributed to an attack of ventricular tachycardia. Consequently, it was advised that he be allowed to resume his work as a steamfitter, under the observation of his own physician. This was done, and, up to the time of this writing, there has been no untoward occurrence.

Comment.—This is another case of short P-R and lengthened QRS intervals, with an attack of tachycardia of ventricular origin. Because the latter occurs in acute coronary thrombosis, and because of the fall in blood pressure and the presence of a leucocytosis, an erroneous diagnosis of myocardial infarction was made. It is most likely that this patient has no organic heart disease, and that the prognosis is very good.

CASE 4.—S. O. S. (Med. No. 47703). This man was first seen on Oct. 22, 1935. He was a powerful man and was employed as a director of athletics. There was no history of rheumatic fever, chorea, venereal disease, or hypertension. A brother is known to have had transient auricular fibrillation without heart disease. Beginning six years earlier, he had had attacks of palpitation which came and ended suddenly, usually during effort, such as playing handball, and lasted about fifteen minutes. He would quickly resume his activities after an attack. At first he thought that the heartbeat was rapid and regular during the attacks, but later, for several years, he felt that the beating was irregular and that the attacks lasted longer. He had been given digitalis and quinidine at different times, but finally became dissatisfied with physicians and took no medication. Despite this he carried on all his duties satisfactorily until August, 1935, when breathlessness on exertion and fatigue, which he had never experienced before, appeared. This grew worse, so that he finally noticed shortness of breath at rest; his weakness increased, and he had to quit his work. It was later learned that a physician had found his heartbeat grossly irregular several months before, and the patient thought that it had been constantly irregular for about six months.

Physical Examination.—The patient was a large, muscular man. The blood pressure was 96/80. The heart was slightly enlarged; the beating was absolutely irregular; the rate was about 130; and there were no murmurs. There were a few râles at the bases of both lungs. The liver was not enlarged, and there was no peripheral edema. The vital capacity of the lungs was 3,900 c.c.

The diagnosis was auricular fibrillation (cause unknown). He was studied at the Peter Bent Brigham Hospital, where the same observations were made. The blood Wassermann reaction was negative. The leucocyte count was 21,900; the urine

and stool were negative. The basal metabolic rate was -13 per cent, and there was no fever. Roentgenologic examination on Oct. 24, 1935 (while he had auricular fibrillation), showed pulmonary congestion and moderate cardiac enlargement, with no prominence of the left auricle. The transverse diameter of the heart was 17.7 cm. On Oct. 31, 1935, when the cardiac mechanism was normal, roentgenograms showed clearing of the lungs and a transverse cardiac diameter of 16.8 cm.

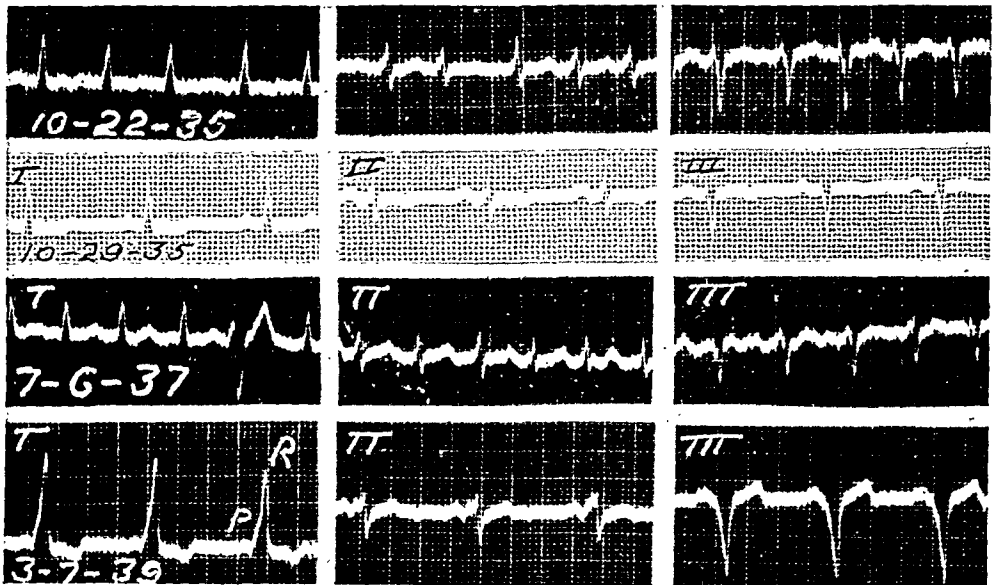


Fig. 4.—Case 4. Upper and third set show auricular fibrillation. Second set shows normal slow rate, with normal P-R and QRS intervals. Lowest set shows regular rhythm, with short P-R and prolonged QRS intervals.

He was given 1.6 Gm. of digitalis during the first two days. The auricular fibrillation continued, but the ventricular rate slowed to about 80. Although he felt much improved, quinidine therapy was started. On the third hospital day he received 0.3, 0.5, and 0.5 Gm. of quinidine at four-hour intervals. The next day he was given 0.7 Gm. in the forenoon and 1.0 Gm. in the afternoon. The fibrillation continued, and the heart rate accelerated considerably. The following day he received 1.0 Gm. four times at four-hour intervals. One hour after the last dose he suddenly became unconscious and had urinary incontinence. He was treated for shock, and was given 0.5 Gm. of caffeine sodium benzoate; in a short time he recovered and appeared to be in good condition. The heartbeat was then found to be slow and regular. During the same day he also received 0.3 Gm. of digitalis. After normal cardiac mechanism had been restored, he was kept on a maintenance dose of 0.2 Gm. of quinidine t.i.d. His improvement was striking; the vital capacity of the lungs rose to 4,800 c.c., all symptoms disappeared, and he returned to his former life of strenuous physical activities.

He has carried on very well during the past five years. At first there were occasional attacks of palpitation which lasted a few minutes, and during a few of these he fainted. Because long periods elapsed when he had no attacks, he had reduced the dose of quinidine to 0.2 Gm. once daily. On one occasion, in March, 1939, an attack of fibrillation lasted for about one week, and he had to take digitalis for a few days, followed by increasing doses of quinidine, to obtain reversion to normal rhythm. Since then, on two doses of 0.2 Gm. of quinidine daily, he has done very well. A roentgenogram on June 3, 1939, showed perfectly normal lungs; the transverse diameter of the heart was 14.8 cm.

Comment.—The electrocardiogram (Fig. 4) shows that this case also belongs to the group with short P-R intervals and prolonged QRS complexes. The attacks of palpitation in this case were of the customary auricular variety; at first he probably had paroxysmal auricular tachycardia, but later it was paroxysmal auricular fibrillation. The important point in this case is that, whereas the latter attacks always lasted only a few minutes, were not incapacitating, and occasionally were accompanied by syncope, he finally developed persistent fibrillation. As a result of the uncontrolled rapid heart rate during months of auricular fibrillation (he was not taking any digitalis), while he was trying to continue an active life, he developed true congestive heart failure. The manifestations of this were dyspnea, pulmonary râles, roentgenologic evidence of congestion of the lungs, and dilatation of the heart. As a result of treatment all evidence of heart failure disappeared; the vital capacity rose from 3,800 to 5,000 c.c.; the transverse cardiac diameter diminished almost 3 cm.; and he has shown no evidence of organic heart disease all these years. This experience demonstrates that, when the heart is normal, heart failure may be brought about by prolonged overwork. A similar case, in which congestive failure resulted from auricular fibrillation when there was no evidence of organic heart disease, was reported by Brill.⁹

SUMMARY

Three cases of Wolff-Parkinson-White Syndrome are described (short P-R and long QRS intervals in patients who are prone to paroxysmal tachycardia, but have no apparent evidence of organic heart disease). Whereas in cases of this type as originally described there were paroxysms of auricular tachycardia or fibrillation, these three patients had paroxysms of ventricular tachycardia. In one case an erroneous diagnosis of acute coronary thrombosis, which it closely simulated, was made. In another case there was evidence of an acute cardiac emergency, and the patient responded promptly to quinidine therapy.

An additional case is described which shows that advanced congestive failure can result, even in the absence of organic heart disease, if a rapid heart rate is permitted to continue for a long time.

These patients present clinical problems that may be serious, and yet are amenable to the proper therapy.

REFERENCES

1. Wolff, L., Parkinson, J., and White, P. D.: Bundle-Branch Block With Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, *AM. HEART J.* 5: 685, 1930.
2. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, *Arch. Int. Med.* 16: 1008, 1915.
3. Wedd, A. M.: Paroxysmal Tachycardia, *Arch. Int. Med.* 27: 571, 1921.
4. Hamburger, W. W.: Bundle-Branch Block: Four Cases of Intraventricular Block Showing Some Interesting and Unusual Features, *M. Clin. North America* 13: 343, 1929.

5. Friedlander, R. D., and Levine, S. A.: Auricular Fibrillation and Flutter Without Evidence of Organic Heart Disease, *New England J. Med.* 211: 624, 1934.
6. Wolferth, C. C., and Wood, F. C.: The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients With Presumably Undamaged Heart, *AM. HEART J.* 8: 297, 1933.
7. Arana, R., and Cossio, P.: Fibrilación auricular y taquicardia ventricular como eventualidad posible en el P-R corto con Q-R-S ancho y mellado, *Rev. argent. de Cardiología* 5: 43, 1938.
8. Hunter, A., Papp, C., and Parkinson, J.: The Syndrome of Short P-R Interval, Apparent Bundle Branch Block, and Associated Paroxysmal Tachycardia, *Brit. Heart J.* 2: 107, 1940.
9. Brill, I. C.: Auricular Fibrillation With Congestive Failure and No Evidence of Organic Heart Disease, *AM. HEART J.* 13: 175, 1937.

Department of Clinical Reports

SIGNIFICANCE OF GENERALIZED SYSTOLIC PULSATION OF VEINS, WITH REPORT OF A CASE IN WHICH THERE WAS MARKED PULSATION OF VARICOSE VEINS

PHILLIP HALLOCK, M.D., AND WILLIAM O. CLARKE, M.D.
MINNEAPOLIS, MINN.

SYSTOLIC pulsation in the peripheral veins has been recognized for many years as a sign of tricuspid incompetency. Benson,¹ in 1836, made a comprehensive study of a case of venous pulsation in the upper extremities, and he appears to have been the first clinician to note that the phenomenon was related to failure of the right ventricle. One year later, King² compiled from the literature a series of cases of pulsating veins, and elaborated further on their cause. In his "Essay on the Safety Valve Function in the Right Ventricle of the Human Heart," he postulated that the inherent weakness of the tricuspid valve acted as a safety mechanism to relieve an overburdened right ventricle. That insufficiency of the tricuspid valve is a cause of pulsating veins is now generally accepted. Since King's communication, other excellent studies have been reported. Kerr and Warren³ reported fifty-six cases in 1925, and very recently White and Cooke⁴ submitted their observations in six cases.

Systolic pulsation of varicose veins has not been observed as commonly. Friedreich,⁵ in 1867, in a review of the literature pertaining to venous pulsation in the extremities, cited Manly, Goubler, and Verneuil, who noted pulsation in the varicose veins of one leg. A few isolated reports have appeared since. Teufl,⁶ in 1936, reported thirty-one cases of pulsating veins; eleven patients in this series showed pulsations of varicose veins in combination with pulsation of other veins. In eight cases the diagnosis was verified by autopsy; either organic or relative tricuspid insufficiency was present. Teufl first stressed the point that if the venous pulsations disappeared with the termination of right-sided heart failure, the lesion was relative tricuspid insufficiency. If, on the other hand, the pulsations persisted after signs of heart failure disappeared, the lesion was organic tricuspid insufficiency.

From the Division of Internal Medicine, University of Minnesota Hospitals, Minneapolis.

Received for publication May 4, 1940.

We have recently had the opportunity to observe a woman, 46 years of age, who presented marked systolic pulsations of the veins of the neck, head, retinæ, and upper extremities, pulsation of the liver, and, finally, marked pulsations of varicose veins of the lower extremities. Our purpose in this report is to call attention to the possible existence of some pathologic condition other than tricuspid insufficiency which may be a factor in producing pulsation of the peripheral veins.

REPORT OF CASE

Mrs. M. S., Case No. 631613, aged 41, a housewife and mother of six children, was first admitted to the University of Minnesota Hospital Oct. 13, 1934. Her chief complaints at that time were intermittent dyspnea on exertion, and edema of the ankles for the preceding seven years. During the three months prior to admission she had been forced to remain in bed because of progressive dyspnea, orthopnea, ascites, and edema. During the preceding five years she had had varicose veins of the lower extremities, and, for four months, a varicose ulcer on her right ankle. There was no rheumatic history. One living sister had "heart trouble." Her mother had died at 80 from heart disease. Her husband and all of her children were living and well except for one son who had questionable heart disease.

Physical examination on admission revealed a well-developed and well-nourished white woman who was moderately dyspneic and orthopneic. The superficial and deep jugular veins were distended and exhibited a systolic pulsation. Ophthalmoscopic examination revealed no abnormalities. A moderate, bilateral hydrothorax was present. The heart was somewhat enlarged, both to the left and right. A systolic thrill was felt at the apex. A loud systolic murmur was heard over the entire precordium, but was maximum over the apex. A presystolic murmur was present over the mitral area. The heart rate was rapid and the rhythm was normal except for a few extrasystoles. The blood pressure was 166/110 on admission. There were an enlarged, tender liver, moderate ascites, and moderate edema of the lower extremities. On the medial aspects of the legs there were pulsating varicose veins; the pulsations were more pronounced on the right, especially in two bulging areas, 2½ cm. in diameter, just below and above the medial aspect of the right knee. Proximal compression of the veins stopped the pulsation. The Trendelenburg test was positive. A varicose ulcer was present on the lateral aspect of the right ankle.

Urinalysis showed a specific gravity ranging from 1.010 to 1.027, and albumin from 0 to 1+. The hemoglobin was 94 per cent, and leucocyte count, 5,200, with 82 per cent neutrophils and 18 per cent lymphocytes. The blood nonprotein nitrogen was 37.8 mg. per cent. The phenolsulphonephthalein test showed a 55 per cent excretion of the dye in two hours. On admission the vital capacity was 1300 c.c. The basal metabolic rate was +5 per cent. The electrocardiogram showed a prolonged P-R interval (0.22 sec.), sinus tachycardia, right axis deviation, a diphasic T₁ and T₂, and low potential in all leads. A teleroentgenogram showed that the total transverse diameter of the chest was 26.5 cm.; the M.L. was 10.0 cm., and the M.R., 7.6 cm. (total 17.6 cm.). Fluoroscopic examination showed that the heart was considerably enlarged, chiefly in the region of the right ventricle and right auricle. The conus pulmonalis was prominent, and there was slight enlargement in the region of the left ventricle.

The treatment consisted of strict bed rest, restriction of salt and fluids, diuretics, sedatives, and full digitalization. Her heart failure disappeared under this regime. However, because of frequent pulsus bigeminy and the onset of auricular fibrillation,

the digitalis was discontinued. The bigeminy persisted, so that digitalis was begun again, and, in addition, the patient was given quinidine, which restored normal rhythm. At the time of discharge, Dec. 16, 1934, the blood pressure was 120/80. The venous pressure was not taken. Unfortunately, no record was made at this time as to whether the pulsation of the veins persisted after the heart failure had been relieved.

The diagnosis at the time of discharge was rheumatic and hypertensive heart disease, marked cardiac enlargement, auricular fibrillation, congestive heart failure, mitral stenosis and regurgitation, relative tricuspid regurgitation, with pulsating veins, and varicose veins of the lower extremities, with a varicose ulcer of the right ankle.

The patient was next seen June 16, 1935, in the Outpatient Cardiac Clinic. She had taken no quinidine for three weeks, and during this period there were numerous extrasystoles. The heart rate was 114 per minute, and auricular fibrillation was present. An orthodiagram showed relatively the same cardiac measurements as on her previous admission.

Her second admission was July 7, 1935. Prior to this the patient had been bed-ridden for three months because of an upper respiratory infection, characterized by a persistent, hacking cough, weakness, and generalized pain, all of which accentuated her cardiac symptoms. No digitalis had been taken during this period.

Physical examination revealed the same abnormalities as on the previous admission, except that there were increased pulsations of the veins of the neck and the varicose veins of the legs. Bilateral hydrothorax was present. The blood pressure was 140/80, and she had auricular fibrillation, with a ventricular rate of 120. The liver was enlarged, and marked edema of the lower extremities was noted.

The laboratory findings were essentially unchanged. The electrocardiogram showed low amplitude of the QRS complexes and auricular fibrillation. The patient was redigitalized, recovered from her heart failure, and was discharged Sept. 11, 1935.

The third admission was on March 3, 1939. Beginning in September, 1938, heart failure had developed gradually, and three weeks prior to admission had become very marked after an upper respiratory infection.

Physical examination revealed a poorly nourished, cyanotic, dyspneic, and orthopneic woman. The superficial veins were distended, and systolic pulsations were noted, especially in the temporal, jugular, basilic, external mammary, crural, and varicose veins of the lower extremities. Ophthalmoscopic examination showed a small patch of retinal atrophy in the right eye and pulsating retinal veins. There was a right-sided hydrothorax, and moist râles were present throughout both lungs. On percussion, the cardiac outline appeared to be larger than before. Systolic and diastolic thrills and murmurs were found over the apical area. The systolic murmur was heard over the entire precordium. The blood pressure was 134/92. Auricular fibrillation was present. The edge of the liver was tender, and could be palpated four fingerbreadths below the right costal margin. Systolic pulsations were seen on inspection and also felt on palpation. Pressure over the liver region accentuated the distention of the jugular veins. Marked ascites and edema of the lower extremities were present. Proximal compression of the superficial saphenous and basilic veins obliterated the distal pulsation of the veins.

The significant laboratory data were as follows: Blood nonprotein nitrogen, 33.6 mg. per cent; total plasma protein, 7.2 Gm., with 3.4 Gm. of albumin and 3.3 Gm. of globulin; cholesterol, 152 mg. per cent; icterus index, 7. Repeated blood cultures were negative. The phenolsulphonephthalein test showed 58 per cent excretion at the end of two hours. The vital capacity was 1100 c.c. Venous pressure measurements were as follows: right antecubital vein, 27 cm. of saline, which, with right upper quadrant pressure, rose to over 40 cm.; left antecubital

vein, 27 cm.; right femoral vein, 34.5 cm.; and left femoral vein, 33.5 cm. The circulation times were definitely prolonged, i.e., arm-to-tongue (decholin), 28 sec.; arm-to-lung, 13 sec. (ether), and lung-to-tongue, 15 sec.

The electrocardiogram showed bigeminy, numerous premature contractions from various foci, and auricular fibrillation. Roentgenograms of the lungs and heart revealed pleural effusion on the right, pulmonary congestion, and massive cardiac enlargement, with a bulge in the region of the conus pulmonalis. Roentgenograms of the tibia and fibula showed no periostitis.

The right pleural sac was tapped. Diuretics, sedatives, and digitalis were given. Thiamin chloride produced no beneficial effect. The venous pressure went as low as 20 cm. of saline in the antecubital veins. The patient gradually improved clinically. Digitalis was discontinued for a time because of toxic signs, both clinical and electrocardiographic, but was begun again later.

A cardiac psychosis developed April 4, 1939. Digitalis was promptly discontinued, and hypertonic glucose solution was given intravenously daily. The icterus index rose to 15, and the van den Bergh reaction became diphasic. On April 26, 1939, the patient was taken home by her husband, against advice.

The diagnosis, in addition to her cardiac condition, was somatic psychosis due to cardiac disease, and icterus due to chronic passive congestion of the liver.

The fourth admission to the hospital was on June 6, 1939. She had taken no digitalis since her previous discharge, and was suffering from severe cardiac failure. The physical signs were essentially the same as on the previous admission. There was marked cyanosis, and auricular fibrillation with a ventricular rate of 140 was present. The blood pressure was 120/70. The total plasma protein was 6.2 Gm., with 2.9 Gm. of albumin and 3.3 Gm. of globulin. The venous pressure was 32 cm. The column of saline in the manometer of the venous pressure apparatus pulsed synchronously with the venous pulsations, and the range of pulsation between systole and diastole was 1 cm. This was the greatest fluctuation of pressure observed at any time. The electrocardiogram and roentgenograms of the chest were unchanged. Repeated blood cultures were negative. On June 7, 1939, the blood nonprotein nitrogen was 54.6 mg. per cent, and the icterus index, 23, with a delayed van den Bergh reaction. The 24-hour urine urobilinogen excretion was 274 mg., indicating severe liver damage.⁷

The treatment, on admission, consisted of paracentesis, oxygen, sedatives, and digitalis. Because of the cardiac psychosis, she was transferred to the psychiatric ward. The venous pressure declined to 17.5 cm. of blood on July 11, 1939, but the pulsation of the veins did not decrease. The patient was again discharged against advice on Aug. 18, 1939.

The fifth admission was on Aug. 28, 1939. Both the cardiac psychosis and cardiac failure were marked. There was infranuclear paresis of the left seventh and twelfth cranial nerves. The venous pressure was 19 cm. of blood, and there was marked pulsatory activity of the veins.

Digitalis and supportive cardiac therapy were begun again. On Aug. 30, 1939, the patient had a cerebral embolus, from the effects of which she recovered uneventfully and rapidly. In addition, both her neurologic and cardiac status improved. The patient was transferred Sept. 14, 1939, to the state hospital, where she died on Dec. 17, 1939.

In résumé, the history dated back twelve years, at which time dyspnea first appeared. Thereafter the clinical picture was one of recurrent and progressive attacks of right- and left-sided cardiac failure. For five years the outstanding clinical feature was tricuspid insufficiency, characterized by increased venous pressure, pulsating liver, and generalized systolic pulsations of the veins, including the varicose veins. Severe cardiac failure and a psychosis were present during the last six months of the patient's life.

The patient died Dec. 17, 1939, at the Fergus Falls State Hospital. Eight hours after death a post-mortem examination was done.* The important abnormalities were as follows: The abdomen was distended and the lower extremities were edematous (about four plus). The peritoneal cavity contained 8000 c.c. of clear, amber fluid. Each pleural cavity contained one liter, and the pericardial cavity, 30 c.c., of a similar transudate. The heart was sent to us for examination. Both lungs were heavy and edematous. The liver had the typical nutmeg appearance. The gall bladder contained gravel-like stones. No arteriovenous aneurysm was found. The brain was not examined.

Examination of the heart† revealed the following: It weighed 395.5 grams after the intrapericardial vessels had been removed and the endocardial surfaces cleaned of blood. Preliminary examination disclosed very slight dilatation of the left atrium and marked dilatation and hypertrophy of the right atrium and right ventricle. The mitral valve was thickened and partly calcified, and the chordae tendineae were shortened and thickened. The lumen was slit-like, and measured 1.2 cm. in length and 0.4 cm. in width, so that there were obviously both mitral regurgitation and stenosis of severe degree. No vegetations were present. The other valves showed nothing of note.

The two atria, with their epicardial tissues, weighed 114 grams. The left atrial muscle appeared normal; the circumference was 20 cm., and the height, 5 cm. The right atrial muscle was markedly hypertrophied; the circumference was 18 cm., but the height was 12 cm.

The epicardial tissues over the ventricles weighed 16 grams—9 grams over the right ventricle and 7 grams over the left. The coronary arteries appeared normal.

The ventricular muscle weighed 265.5 grams. The right ventricle weighed 153.3 grams, and the thickness of its free wall varied from 0.3 cm. at the base to 0.2 cm. near the apex; the left ventricle weighed 112.2 grams, and the thickness of its wall varied from 1.8 cm. to 0.6 cm. The relative weight of the right to the left ventricle was 1.4:1.

The pulmonary conus was elongated; it measured 5.4 cm., and its width was increased to 11.0 cm. The ostium of the tricuspid valve was 11.9 cm., and that of the pulmonary valve, 8.4 cm. The mitral ostium was 5.2 cm., and the aortic, 6.6 cm. The inflow tract of the right ventricle measured 6.8 cm., and the outflow tract, 10.4 cm. On the left side the inflow tract was 6.9 cm., and the outflow tract, 7.7 cm.

DISCUSSION

During the clinical observation of this patient we were inclined toward a diagnosis of organic tricuspid insufficiency, rather than relative tricuspid insufficiency. Our only reason was the fact that the pulsations persisted after the venous pressure fell. This was not conclusive evidence, however, for the venous pressure never did return to normal limits. At necropsy the tricuspid leaflets appeared normal, but of much more interest was the fact that the tricuspid orifice was only slightly, but sufficiently, dilated to give rise to relative tricuspid insufficiency. We have noted the condition of the tricuspid ring in numerous cases of congestive failure in which the degree of stretching was as much or

*We are indebted to Dr. Stanley Lindley and Dr. R. Reader, of the Fergus Falls State Hospital, who did the autopsy and kindly sent us the heart for further examination.

†We are indebted to Dr. B. J. Clawson, of the Department of Pathology, who made the gross examination of the heart, and to Dr. George Higgins, pathologist at the Glen Lake Sanatorium, who dissected the heart chambers and made careful measurements of the cardiac structures.

greater than in this case, yet no pulsation of the veins was present during life.

It would thus seem highly improbable that the marked venous pulsations in this case are to be explained as a result of the tricuspid insufficiency alone.

Another outstanding feature of this case was the minimal dilatation of the left atrium, in spite of the severe grade of mitral stenosis. This suggested that there was some impediment to the volume flow of blood through the pulmonary circuit.

From a consideration of these points, it would appear that some other condition was responsible, in part, for the marked pulsation of the veins. This could be explained best by some factor which would set up resistance to the flow of blood through the lesser circulation. The most obvious explanation would appear to be narrowing of the pulmonary vascular bed. It is well recognized that secondary arteriosclerotic changes may occur in the pulmonary vessels in long-standing cases of mitral stenosis. An abundance of evidence is found in the literature to support this view.⁸⁻¹³ At times the pulmonary sclerosis may be marked, with involvement of the large, medium-sized, and small vessels, which results in narrowing of the vascular bed. This is especially true when a "button-hole" mitral stenosis exists.¹⁴ The effect of these changes would be to increase greatly the right intraventricular pressure. With the inception of relative tricuspid insufficiency, the release of the pulse wave into the venous system is made possible by a vigorously contracting right ventricle. Although proof of pulmonary artery narrowing is lacking in this case because the lungs were not available for study, it is reasonable to assume that such a condition could exist, and that this, in addition to relative tricuspid insufficiency, could very well explain the marked retrograde transmission of the pulse wave from the right ventricle. Careful anatomic examination of the pulmonary vascular tree should be made in all cases of tricuspid insufficiency in which pulsation of veins was present during life.

CONCLUSIONS

1. A case of marked, generalized, systolic pulsation of veins is presented. Striking pulsations of the varicose veins in the lower extremities were an outstanding feature.

2. This study suggests that a pulmonary factor may play an important role in the mechanism which is responsible for systolic pulsation of peripheral veins.

REFERENCES

1. Benson: *Dublin L. Med. & Chem. Sc.* 8: 324, 1836.
2. King: *Guy's Hosp. Rep.* 2: 104, 1837.
3. Kerr, W. J., and Warren, S. L.: *Peripheral Pulsations in the Veins in Congestive Failure of the Heart Associated With Pulsation of the Liver and Tricuspid Regurgitation*, *Arch. Int. Med.* 36: 593, 1925.

4. White, P. D., and Cook, W. T.: Recognition and Significance of Marked and Chronic Systolic Pulsation of the Deep Jugular Veins, Transactions of Association of American Physicians, Dorran, Philadelphia 54: 199, 1939.
5. Friedreich, N.: Handb. d. spec. Path. u. Therap. 5: 192, 1867.
6. Teuff, R.: Pulsation normaler and varikoser Extremitätenvenen und ihre diagnostische Bedeutung, Wien. med. Wchnschr. 86: 436, 1936.
7. Watson, C. J.: Studies of Urobilinogen. II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, Arch. Int. Med. 59: 196, 1937.
8. Lyungdahl, W.: Untersuchungen über die Arteriosklerose der kleinen Kreislaufs, 1915, Verlag von J. F. Bergmann.
9. Posselt, Adolf: Die Erkrankungen der Lungenschlagader, Ergeb. d. allg. Path. u. path. Anat. 13: 298, 1909.
10. Zeckr P.: Atheroma and Its Sequelae in Rheumatic Heart Disease, Am. J. M. Sc. 184: 356, 1932.
11. Steinberg, U.: Ueber secundäre Pulmonal Arteriosklerose, Beitr. z. Path. 82: 307, 1929.
12. Brenner, O.: Pathology of Vessels of Pulmonary Circulation, Arch. Int. Med. 56, parts III and V, 1935.
13. Gouley, B. A.: Role of Mitral Stenosis and of Post-Rheumatic Pulmonary Fibrosis in the Evaluation of Chronic Rheumatic Heart Disease, Am. J. M. Sc. 196: 11, 1938.
14. Parker, F., and Weiss, Soma: Nature of Significance of the Structural Changes in the Lung in Mitral Stenosis, Am. J. Path. 12: 573, 1936.

LEUCEMIC PERICARDITIS

REPORT OF A CASE OF LYMPHATIC LEUCEMIA IN WHICH MASSIVE PERICARDIAL EFFUSION WAS THE EARLIEST AND MOST OUTSTANDING MANIFESTATION

MARTIN H. WENDKOS, M.D.
PHILADELPHIA, PA.

INTRODUCTION

INVOLVEMENT of the heart by infiltration into the pericardium and myocardium by retrograde extension from adjacent diseased lymph nodes has already been described in cases of lymphosarcoma^{1, 2} and tuberculosis.³ Although similar involvement of the heart can occur in lymphatic leukemia,⁴ we are not aware of a reported instance in which a massive pericardial effusion secondary to leucemic infiltration of the pericardium constituted the first clinical manifestation of the leucemic state. We therefore wish to report the following case of leucemic pericarditis, not only because of its rarity, but because it simulated in many ways the so-called "clinically primary" tuberculous pericarditis, and therefore serves to emphasize certain criteria which should be fulfilled before the diagnosis of the latter condition can be made with certainty.

CASE REPORT

M. McG., a colored girl, 15 years of age, was originally admitted to the Frederick Douglass Memorial Hospital on the medical service of Dr. Truitt and Dr. Greene on September 17, 1937. Several weeks before admission she had developed an unproductive cough and weakness, followed by a progressive weight loss, anorexia, dyspnea on very slight exertion, and fever. The outstanding features of the physical examination were as follows: the patient was undernourished, breathless (respiratory rate, 36), febrile (temperature 102° F.), and obviously acutely ill. The veins of the neck were engorged in both the sitting and supine positions. No cervical lymph nodes were palpable. There was diffuse enlargement of the cardiac area both to the right and left, with widening of the area of supracardiac dullness. The latter was more marked in the supine than in the upright position. The apex beat was not palpable and the heart sounds were muffled. The rhythm was normal, and no murmurs or pericardial friction rub were audible. The blood pressure was normal (110/80). A rather marked paradoxical pulse was present. The abdomen and extremities were essentially negative except for a moderate degree of wasting. Under the fluoroscope, the cardiac shadow was seen to be considerably enlarged, but no cardiac contractions were visible. In addition, it was noted that the supracardiac shadow was widened and that the mediastinal lymph nodes were enlarged. The electrocardiogram showed deeply inverted T waves in all the limb leads. The blood cell count was normal except for a slight secondary anemia. The leucocytes numbered 7,500, and the differential count was normal. On the basis of the history, physical signs, and laboratory data, a diag-

From the Division of Cardiology of the Philadelphia General Hospital and the School of Medicine of the University of Pennsylvania.

Received for publication May 25, 1940.

nosis of tuberculous pericardial effusion was made. On September 18, 1937, the first pericardial paracentesis was performed. This yielded 500 c.c. of amber-colored, slightly cloudy fluid. A corresponding amount of air was injected. A second fluoroscopic study, after the establishment of the pneumopericardium, clearly showed the widened supracardiac shadow, the enlarged hilar lymph nodes, the thickened pericardium, and the small heart. Although this combination of signs has been considered characteristic of tuberculous pericarditis, examination of a smear made from the pericardial fluid failed to reveal any tubercle bacilli. A guinea pig was therefore inoculated with the fluid on the same day.

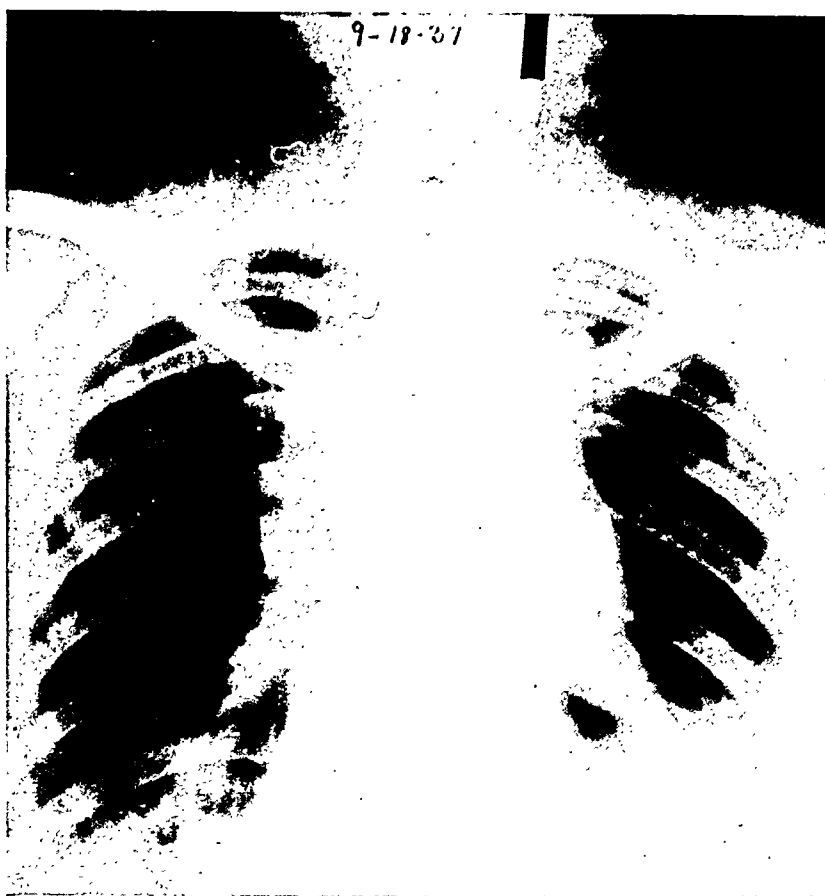


Fig. 1.—Roentgenogram after pneumopericardium. Note the enlarged mediastinal nodes, widened supracardiac shadow, thickened pericardial sac, and small heart.

On September 27, 1937, a second pericardial paracentesis was performed; a total of 700 c.c. of fluid, now serohemorrhagic in character, was removed, and a corresponding amount of air injected. The roentgenogram which was taken after this procedure is shown in Fig. 1. In smears made from this fluid it was again impossible to demonstrate the presence of tubercle bacilli, and a second guinea pig was therefore inoculated. The patient subsequently developed a left-sided pleural effusion which was tapped by Dr. Greene on September 30, 1937, and 950 c.c. of serosanguineous fluid were removed. This was stained and examined for tubercle bacilli, with negative results. Subsequently, the patient had fever of an intermittent type, and repeated reaccumulations of fluid in the left side of the chest; the latter was tapped at frequent intervals. Physical examination, fluoroscopic study, and roentgenograms of the chest failed to reveal any evidence of a reaccumulation of fluid in the pericardial cavity. On November 11, 1937, the guinea pigs were sacrificed and examined. No evidence of tuberculosis was found.

On November 12, 1937, the patient left the hospital with a final diagnosis of pericarditis and pleurisy with effusion, probably tuberculous in origin. After remaining at home for four days, she was admitted to the medical service of Dr. David Riesman at the Philadelphia General Hospital on November 16, 1937. Physical examination at this time revealed that the patient had obviously lost more weight, although she did not appear to be acutely ill. A fever of 102° F. was present. Lymph nodes were easily palpable in the neck, both axillae, and

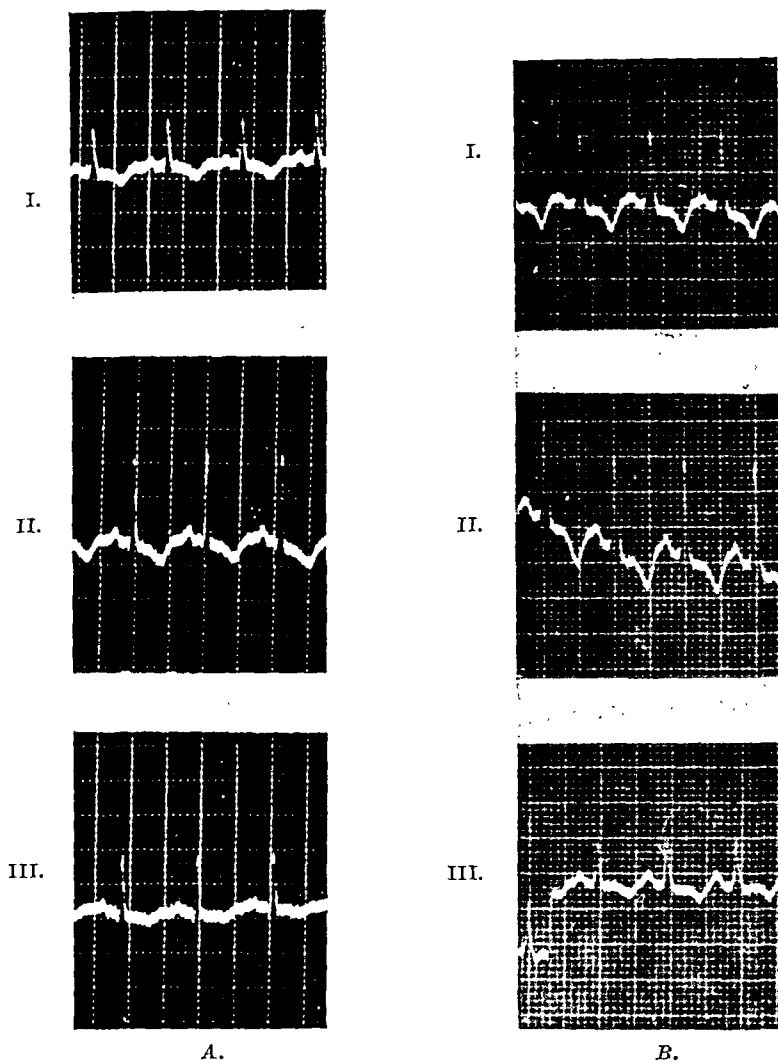


Fig. 2.—Electrocardiograms taken—A, While there was a large effusion. B, When there was no effusion. Note inverted T waves in all the limb leads, and that there is no material difference between the two tracings.

in the inguinal regions. Signs of fluid in the left side of the chest, with displacement of the heart to the right, were readily evident. The heart presented nothing remarkable except for simple tachycardia and a widened area of supracardiac dullness. The edge of the liver was felt at the level of the umbilicus, and the edge of the spleen was palpable on deep inspiration. The sternum was very sensitive to palpation and percussion. The electrocardiogram was similar to the one taken at the Douglass Hospital; it showed inverted T waves in all the limb leads (Fig. 2). Roentgenograms of the chest revealed a large pleural effusion on the left side, with displacement of the normal-sized heart and mediastinum to the

right. The following day, another roentgenogram, taken after the removal of 700 c.c. of pleural fluid, showed that the base of the heart and upper mediastinum were considerably widened as a result of enlarged lymph nodes. A diagnosis of "tuberculous mediastinal adenitis, or some form of lymphoblastoma" was made by the roentgenologist. The leucocytes, the day after admission, numbered 116,000, of which 97 per cent were lymphocytes. Two days later the leucocyte count had risen to 191,000, all of which were lymphocytes. A biopsy of one of the inguinal nodes revealed histologic changes typical of lymphatic leucemia. Before any further studies could be carried out, the patient died suddenly and unexpectedly on November 25, 1937.



Fig. 3.—Section through myocardium. Note leucemic infiltration extending into myocardium, through its lymphatics ($\times 92$).

An autopsy was performed by Dr. Harold Johnson on the same day, and the following notes were made: "After the chest was opened, the mediastinum was seen to be considerably widened as a result of infiltration of gray-white tissue in which lymph node outlines could be vaguely recognized. This infiltration extended down over the parietal pericardium. The parietal pericardium was loosely adherent to the visceral pericardium, because of an infiltration of similar tissue into the visceral pericardium. This was rough and shaggy, in areas. There was no excessive amount of fluid in the pericardium. The heart was of normal size and weighed 330 grams. The myocardium was a pale pink in color, and through this there was a heavy mottling of gray-white areas. The heart was otherwise normal. The left lung was collapsed, and its pleural surface was irregularly thickened with opaque nodules. Within the left pleural cavity there were 800 c.c. of serosanguineous fluid. The right lung was normal. The spleen weighed 120 grams, its parenchyma was soft, its cut surface was pale red, and it was peppered with gray-white spots throughout. The left kidney showed a few bulging, red,

speckled nodules on its surface. The bone marrow from the vertebrae and the femur was grayish red and soft. The lymph nodes along the aorta, in the mediastinum, mesentery, and subcutaneous regions were all enlarged, firm, and gray-white in color." The diagnosis from these gross abnormalities was as follows:

1. Leucemic infiltration into the pericardium, myocardium, left pleura, spleen, liver, kidney, lymph nodes, and mediastinum.
2. Hyperplasia of the bone marrow.

Gross examination of the brain by the neuropathologist, Dr. Helena Riggs, showed chronic passive congestion. Histologic examination of sections from various organs confirmed the gross diagnosis. The infiltration into the myocardium is seen in Fig. 3.

DISCUSSION

A large leucemic pericardial effusion, such as was encountered in this case, does not present itself often. From the point of view of frequency, therefore, the lesion is not a very important one. When it does occur, its diagnosis will probably not be as difficult as it was in this instance. Its recognition will depend, first, upon the diagnosis of the pericardial effusion, and, second, on discovery of the leucemic state. The mistake here occurred because the leukemia, early in the course of the disease, was unaccompanied by the usual leucocytosis, hemorrhagic tendencies, and lymph node enlargement. However, the purpose of this report is not to emphasize the difficulties in the diagnosis of leucemic pericardial effusion, but rather to show that, because of the insidious onset of the illness, the fever without a corresponding leucocytosis, the massive serosanguineous pericardial effusion, the small heart, the absence of cardiac murmurs, the T-wave changes in the electrocardiogram, and the supposedly associated tuberculosis, as represented by the enlarged mediastinal lymph nodes, there was in this case a group of abnormalities which are recognized as characteristic of tuberculous pericarditis.^{5, 7-10} However, the failure to demonstrate the tubercle bacillus in the pericardial fluid proved to be significant in this instance. The conclusion is therefore warranted, from this experience, that reservations should be placed upon the diagnosis of tuberculous pericarditis when the causative organism cannot be recovered from the pericardial effusion, even though some observers⁹ consider that associated mediastinal disease is of equal etiologic significance.

SUMMARY

1. A case of lymphatic leukemia is reported, in which a massive pericardial effusion, simulating the tuberculous variety, was the only striking abnormality early in the course of the disease.

2. The difficulty in making the correct diagnosis during the aleucemic stage is discussed.

3. The subsequent development of enlarged lymph nodes and the characteristic leucocytosis enabled a correct diagnosis to be made before death, and this was confirmed by necropsy.

4. Emphasis is placed upon the necessity of demonstrating the tubercle bacillus in the pericardial fluid, whenever a diagnosis of tuberculous pericarditis is entertained.

We wish to thank Dr. David Riesman for permission to report this case, and to acknowledge the cooperation of the Division of Pathology in the preparation of the report.

REFERENCES

1. Wolf and Giet: Invasions of the Myocardium From Mediastinal Lymphosarcoma, *Bull. et Mémoires de la Société Anatomique de Paris* 92: 340, 1922.
2. Siegel, M. L., and Young, A. M.: Electrocardiographic Findings in Tumors of Heart, With Report of Case, *AM. HEART J.* 8: 682, 1933.
3. Gouley, B. A., Bellet, S., and McMillan, T. M.: Tuberculosis of Myocardium: Report of Six Cases, With Observations on Involvement of Coronary Arteries, *Arch. Int. Med.* 51: 244, 1933.
4. Forkner, C. E.: *Leukemia and Allied Disorders*, Macmillan, 1938.
5. Riesman, D.: Primary Tuberculosis of the Pericardium, *Am. J. M. Sc.* 122: 6, 1901.
6. Clarke, J. A., Jr.: Clinically Primary Tuberculous Pericarditis, *Am. J. M. Sc.* 177: 115, 1929.
7. Kornblum, K., Bellet, S., and Ostrum, H. W.: Tuberculous Pericarditis: Its Roentgenologic Significance, *Am. J. Roentgenol.* 29: 203, 1933.
8. Bellet, S., McMillan, T. M., and Gouley, B. A.: Tuberculous Pericarditis: Clinical and Pathologic Study Based Upon Series of Seventeen Cases, *M. Clin. North America* 18: 201, 1934.
9. Harvey, A. M., and Whitehill, M. R.: Tuberculous Pericarditis, *Medicine* 16: 45, 1937.
10. Bellet, S., and McMillan, T. M.: Electrocardiographic Patterns in Acute Pericarditis; Evolution, Causes and Diagnostic Significance of Patterns in Limb and Chest Leads; Study of 57 Cases, *Arch. Int. Med.* 61: 381, 1938.

Department of Reviews and Abstracts

Selected Abstracts

Hill, W. H. P., and Andrus, E. C.: The Cardiac Factor in the "Pressor" Effects of Renin and Angiotonin. *J. Experimental Med.* 74: 91, 1941.

Upon the isolated hearts of cats perfused with Ringer-Locke solution, renin produced no significant effect. Angiotonin, on the other hand, brought about decrease in coronary flow and increase in amplitude of beat without any consistent effect upon heart rate.

Both renin and angiotonin augmented the cardiac output and raised the "arterial" pressure in the Starling heart-lung preparation; here too without influence on the heart rate.

Electrocardiograms recorded before, during and after the pressor effects of renin and angiotonin in the anesthetized cat showed no abnormalities until the blood pressure had risen above 190 mm. Hg when various types of cardiac arrhythmias appeared. These were prevented, or normal rhythm was restored, by cutting the vagus nerves or injecting atropine.

It is concluded that the "pressor" effects of renal pressor substances include direct stimulation of the myocardium and augmentation of ventricular beat. Unless these actions lead to excessive decrease in diastolic volume of the ventricles, the cardiac output will be increased. The significance of this in the production of the pressor effect is discussed.

AUTHORS.

Strombeck, J. P.: Effects of Arterial Resection. *Experimental Angiographic Study.* *Acta chir. Scandinav.* 83: 510, 1940.

The animal experiments carried out by Leriche's co-workers, Fontaine and Schnatter, with the view to showing the mode of action of arterial resections, have been checked by using a technique more free from objections. Resections of thrombotic portions of arteries showed no reliable effect as demonstrated by arteriograms.

AUTHOR.

Karsner, H. T., Simon, M. A., and Fujiwara, T. F.: Relation of Experimental Pulmonary Arterial Hypertension to Arteriosclerosis. *Arch. Path.* 31: 585, 1941.

What is probably a slight degree of pulmonary arterial hypertension, lasting over many months, is induced by the lodgment of large numbers of small seeds in the small arteries and arterioles of the lungs of the dog. The evidence of such hypertension is found in the squaring of the ends and the increase of the transverse diameters of the nuclei of the cardiac muscle. The probable slight increase of pressure, persistent and prolonged, does not cause pulmonary arteriosclerosis.

AUTHORS.

Feldt, R. H., and Wenstrand, D. E. W.: The Cold Pressor and the Breath-Holding Test. An Analysis of Results in Two Hundred Subjects. *Arch. Int. Med.* 67: 1157, 1941.

In the present series of 200 cases the mean responses of the blood pressure to the cold pressor test and the breath-holding test were similar except that breath holding obtained a slightly greater systolic reaction among normal hyporeactors. In most of our subjects the response to the cold pressor test was the same as or higher than the response to the breath-holding test. Wide differences between the reaction to the cold pressor test and the reaction to the breath-holding test were at times found in the same person. Hyperreaction to cold was found in thirty-nine subjects who were hyporeactors to breath holding. Hyperreaction to breath holding was found in sixteen subjects who were hyporeactors to cold.

AUTHORS.

Scuderi, Carlo S.: Fat Embolism: A Clinical and Experimental Study. *Surg., Gynec. and Obst.* 72: 732, 1941.

After injury to bone marrow fat or adipose tissue, there is a disintegration of the supporting fibrous tissue with liberation of fat. Naturally there are ruptured blood vessels in the vicinity of the injury. The arteries squirt more blood into the area, thereby increasing the pressure, while the veins remain open and absorb the fatty mixture by venous suction. Fat embolism is more common in fracture than in any other condition because the veins are encased in a bony wall and hence cannot collapse as elsewhere in the body; thus they remain wide open for the admittance of the fatty mixture. Death from fat embolism is not common after fractures. Grondahl states that the occurrence is fatal in only 1 out of 300,000 fractures.

There is no clinical correspondence between the apparent injury and the degree of resulting lipemia. Injuries which are apparently identical may in one individual be followed by a fatal lipemia, while in another the same injuries may cause but a slight disturbance. The onset may be sudden, within a few hours of the injury, but usually does not become manifest until the third or fourth day. Once the symptoms set in, they may vary from a slight irritability and excitability to maniacal periods associated with high grade delirium and death. In the more severe cases dyspnea appears with gradual passive congestion of the lungs as more capillaries are obstructed. A cough of productive nature may appear and lead to a diagnosis of bronchopneumonia.

The majority of cases of fat embolism are so mild that they do not cause symptoms, or so severe that death results in a few days from involvement of the lungs or the brain. During life the diagnosis is justified only if there is a history of an injury, with the typical clinical manifestations. Confirmatory signs are the presence of fat in the urine, the demonstration of fat emboli in the retinal vessels, and the appearance of petechial hemorrhages in the chest, shoulders, and neck.

The prognosis in fat embolism should always be reserved because some of the patients who appear to be coming along well suddenly grow worse and die. Most of the patients recover, but due to the fact that only the fatal or very sick cases are diagnosed and the mild cases overlooked, most people have the reverse idea.

Since all the bone marrow fat extracted from a femur is not sufficient to cause death, the author believes, from experimental evidence, that oleic acid, one of the split products of the neutral olein of bone marrow, is the probable etiologic agent. This substance is seven times as lethal as neutral bone marrow fat and sufficient quantity could easily be available.

M. NAIDE.

Cooke, W. T., and White, P. D.: Auricular Fibrillation Following the Injection of Acetyl-B-Methyl Choline Chloride (Mecholyl) During an Attack of Paroxysmal Auricular Tachycardia or Flutter. *Cardiologia* 4: 313, 1940.

In a new case of paroxysms of tachycardia with an electrocardiogram showing short P-R intervals and wide QRS complexes and otherwise normal heart (type described by Wolff, Parkinson, and White), auricular fibrillation of one and one-half hours' duration was produced during an attack of paroxysmal auricular tachycardia (or flutter) by an injection of acetyl-B-methylcholine chloride (5 mg.).

AUTHORS.

Kisch, B.: The Changes of the Chest-Leads of the Electrocardiogram Due to Damage of the Heart's Surface. *Cardiologia* 4: 318, 1940.

A small damage concerning the contractility of the surface layer of the heart muscle produced experimentally by local KCL application is sufficient to change the chest lead electrocardiogram in a high degree, even if the standard electrocardiogram leads show no remarkable changes.

In a right side damage the right chest lead is more changed than the left chest lead and vice versa.

If the damage is strictly limited to one side of the ventricle, there is a lifting of S, the S-T segment and T in the homolateral chest lead and a depression of the same parts of the electrocardiogram in the heterolateral chest lead.

Should both parts of the ventricle be damaged, mixed effects result which depend on the place and the size of the damage.

Experiments on the frog's heart, which has only one ventricle, proved, that also in our other animal experiments the changes produced in the chest lead are not to be referred to changes in the behavior of the right or left chamber in an anatomic sense, but only to a change in the behavior of the right or left part of the surface layer of the heart muscle.

These experiments show clearly the importance of taking at least a right and a left chest lead in all cases of clinical investigations, for arriving at more exact diagnosis.

AUTHOR.

Teran, V. S.: Three Observations on Complete Intermittent Auriculo-Ventricular Block. *Rev. argent. de cardiol.* 7: 374, 1941.

Three observations of intermittent complete heart block are reported, one of them with a manifest vagal factor in its production.

A curious form of auricular arrhythmia was observed in the course of ventricular arrest in one of the observations.

The ventricular complexes during complete block showed as compared with those during sinus rhythm; increase in amplitude and duration of QRS, longer duration of ST, and increase in size of the T wave.

AUTHOR.

Cohen, L., Gray, I., Nash, P. I., and Fink, H.: Calcareous Aortic Stenosis: Report of Nine Cases With Autopsy Findings. *Ann. Int. Med.* 13: 2091, 1940.

Calcareous aortic stenosis is a disease predominantly affecting males and usually occurring past middle life, but occasionally encountered in younger persons. The outstanding physical signs are the typical murmur, accompanied by a diminished second aortic sound and a palpable thrill over the aortic area. The heart is enlarged. The stenotic aortic lesion is usually accompanied by changes (atheromatous) in the

aorta and coronary arteries and at times by calcific changes in the mitral valve and ring. The syndrome of angina pectoris and disturbances in cardiac rhythm are commonly seen in this disease. The occurrence of sudden death is a striking and frequent characteristic.

In this communication nine cases of calcareous aortic stenosis have been reported and the etiologic factors, morphologic changes, and clinical features have been discussed.

AUTHORS.

Bain, C. W. C., and Wray, S.: Ruptured Aortic Valve With Mycotic Aneurysm Due to Acute Bacterial Endocarditis. Brit. Heart J. 3: 132, 1941.

A case of rupture of the aortic valve with a mycotic aneurysm due to bacterial endocarditis has been described. The temperature was subnormal throughout the illness. Death took place quickly with signs of left ventricular failure.

AUTHORS.

Denenholz, E., and Rambar, A. C.: Rheumatic Fever in a Newborn Infant. Am. J. Dis. Child. 61: 1044, 1941.

A case of probable rheumatic fever in a breast-fed infant, 10 days old, is reported.

Stone, S.: Treatment of Sydenham's Chorea by Fever and Vitamin B Therapy. New England J. Med. 223: 489, 1940.

Twenty patients with severe, moderately severe, and mild cases of Sydenham's chorea were treated. Five of the seven cases received artificial fever therapy, together with vitamin B complex given orally and thiamin chloride given parenterally. One severe and one moderately severe case received thiamin chloride parenterally and vitamin B complex orally, while all the others received oral medication only.

In the electropyraxia-treated cases recovery was produced with about fourteen hours of fever at 104° F. or over. When this was combined with vitamin B therapy, advanced cardiac conditions were found to be no contraindication to the fever treatment. Usually a change for the better in the carditis was noted at the end of the treatment.

One of the two cases treated with thiamin chloride responded with cessation of symptoms after the second intravenous injection of 10 mg. of the drug.

Various degrees of behavior disturbances were seen in most of the moderately severe and milder cases. They all received 4 to 8 c.c. of vitamin B complex orally, three times daily. The improvement in physical manifestations was less rapid than it was in the fever-treated cases, but most of the symptoms disappeared within one month. No hospitalization was required for any patients in this group. Improvement was noted in their behavior concomitantly with the change for the better in the choreic manifestations.

AUTHOR.

Landis, E. M.: Hypertension and the Pressor Activity of Heated Extracts of Human Kidneys. Am. J. Med. Sc. 202: 14, 1941.

Heated kidney extracts were prepared from tissue obtained at autopsies of sixteen cases with normal blood pressure during life and of thirty-four cases with marked hypertension. Anesthetized, nephrectomized rabbits were used for assay. Kidney extracts prepared from cases of benign hypertension and chronic glomerulonephritis were not more active than those of normal kidneys. The four extracts which showed pressor activity outside the normal range all came from cases of malignant nephro-

sclerosis. Nevertheless, the variations in activity, even in this group, make it impossible to demonstrate by these methods any clear relation between blood pressure during life and the renin content of kidney tissue after death.

The rise in blood pressure produced by active extracts of human kidneys is similar to that observed with renin from other species in that the blood pressure of the unanesthetized rabbit rises without a decrease of peripheral blood flow.

AUTHOR.

Cameron, D. E., and Rosen, S. R.: The Reactivity of Intracranial Vessels in the Aged. *Am. J. M. Sc.* 201: 871, 1941.

A method is reported for investigating the reactivity of the cerebral vessels by observation of the spinal fluid pressure changes after intravenous injections of histamine.

A series of thirty-eight senile and fifty-five psychiatric patients at younger age levels was examined.

The average rise in spinal fluid pressure in the senile group was 34 mm. of water; the average for twenty-nine alcoholics included in the younger group was 86 mm. of water, and the rise for the twenty-six remaining patients in the younger group was 70 mm. of water.

The bearing which this may have on possible cerebral anoxemia in the aged was considered.

AUTHORS.

Montgomery, L. C.: A Case of Multiple Arterial Thrombosis Occurring in a Professional Blood Donor. *Canadian M. A. J.* 44: 289, 1941.

A case is reported of a man, aged 44 years, a professional donor for three years, who developed a hemiplegia following the giving of a transfusion of 500 c.c. of blood. He had given 375 c.c. five days previously. Fifteen days after the hemiplegia he developed thrombosis of the splenic artery and while still in the hospital mesenteric thrombosis occurred. The latter two arterial thromboses were confirmed at operation and autopsy. The author suggests limiting the number of transfusions which a professional blood donor may give within a specified time. No prothrombin time was done on this patient.

M. NAIDE.

von Hofer, H.: The Influence of Gas-Mask Breathing on the Circulation of Men. *Cardiologia* 4: 331, 1940.

The influence of the gas mask on the circulation, especially on the electrocardiogram, was tried in fifty persons. Changes were found in respiration, pulse rate, blood pressure and electrocardiogram. They were fairly the same as after mild exercise.

Conclusions were drawn that the gas-mask breathing is well endured by normals, but in cardiacs some damage must be assumed.

AUTHOR.

Veal, J. Ross, and Hussey, Hugh Hudson: The Venous Circulation in the Lower Extremities During Pregnancy. *Surg., Gynec. and Obst.* 72: 841, 1941.

The assumption that postural dependent edema and varicose veins of the lower extremities in pregnant women are due to localized obstruction of the deep veins is supported by the types of pressure curve obtained when popliteal venous pressures are recorded during exercise.

The factors responsible for increasing the degree of localized venous obstruction in some pregnant women to the extent of causing edema or varicose veins or both are not perfectly understood. The size and position of the uterus are factors of recognized importance.

In pregnant women manifesting significant obstruction of the femoro-iliac veins, provision of adequate support for the superficial veins by means of elastic stockings minimizes or prevents the development of varicose veins.

AUTHORS.

Glaser, S. Thomas, and Lesser, Albert: **Femoral Vein Ligation for Chronic Occlusive Arterial Disease.** *Am. J. Surg.* 52: 100, 1941.

Twenty cases of occlusive arterial disease of the lower extremities in which femoral vein ligation was performed have been presented and studied with follow-up for periods ranging up to two years. Definite relief of pain has been effected by this procedure in the majority of cases studied. Local demarcation and spontaneous separation of gangrenous tissue has been facilitated by femoral vein ligation in at least ten out of seventeen cases of gangrene.

The opening up of new collateral vessels is believed to have been produced and was satisfactorily demonstrated in at least two cases. Restoration of pulsation of the femoral artery was demonstrated in two cases after femoral vein ligation. There were no harmful or untoward effects as a result of the venous stasis produced. Femoral vein ligation is a simple procedure, easily performed under local anesthesia and unattended by any morbidity or mortality.

We believe this procedure to be of definite value in impending or early minimal gangrene of the lower extremities in the chronic occlusive arterial diseases.

AUTHORS.

Mulholland, John H., and Rovenstine, E. A.: **Surgery in the Carotid Sinus Syndrome.** *Surgery* 9: 751, 1941.

The procedures employed in the diagnosis, preoperative care, anesthetic management, and operation in the carotid sinus syndrome are described. Mention is made of the clinical application of knowledge of this reflex area. Five cases are cited briefly. The symptoms of hyperactive carotid sinus reflex may be relieved by surgical denervation of the sinus.

AUTHORS.

Gray, Howard K., and Skinner, Ira C.: **Constrictive Occlusion of the Superior Vena Cava.** *Surg., Gynec. and Obst.* 72: 923, 1941.

Three cases of constrictive occlusion of the superior vena cava in which the patients were treated by operation have been reported. In two of these there was probably an associated thrombosis, in the other the constriction was caused by a mass of calcified tuberculous glands. Mediastinotomy with the release of the constrictive bands seems indicated in those cases of superior vena caval obstruction in which the venous pressures are increasing and in which the symptoms are progressing.

AUTHORS.

Evans, W., and Paxon, T.: **A Comparison of the Mercurial Diuretics Used in Heart Failure.** *Brit. Heart J.* 3: 112, 1941.

Certain mercurial diuretics were submitted to a clinical trial in fifty patients with heart failure, for the purpose of deciding their relative diuretic potency. The

best method of administering them was also investigated, as well as the best means of augmenting their natural diuretic action. Esidrone, mersalyl, neptal, and salyrgan were given in 2 c.c. doses intravenously (197 times), and intramuscularly (110 times). Mersalyl, neptal, and salyrgan were tried orally in tablet form, and novurit and salyrgan were tested as a rectal suppository. Eleven methods of enhancing the diuretic effects of mercurial salts were also tested, and 507 observations were devoted to this problem. The results of this investigation are as follows:

Neptal and esidrone when given intravenously or intramuscularly produced the largest diuresis, rather larger than salyrgan and much larger than mersalyl.

The intravenous method almost always induced greater diuresis (average diuretic index of 76) than the intramuscular method (average diuretic index of 56).

Of the two rectal suppositories tried, novurit gave much better results than salyrgan.

Neptal tablets by mouth proved more efficient (average diuretic index of 32) than mersalyl tablets (average diuretic index of 19), salyrgan tablets, or novurit suppositories rectally (each with a diuretic index of 17). Ammonium chloride was always given in association.

Although the urinary output after oral administration of a mercurial salt was greatest when 0 to 48 Gm. (three new tablets) of neptal were used, satisfactory diuresis was also produced by 0.32 g. (two new tablets).

Thirty grains (2 Gm.) of ammonium chloride given two hours before the administration of a mercurial preparation proved to be the best form of premedication. Enteric chocolate-coated tablets, each containing 7.5 grains (0.5 Gm.), proved the most convenient form of dispensing ammonium chloride.

In a patient confined to bed with heart failure and especially with edema, standard treatment would include the injection of a mercurial diuretic (2 c.c.) intravenously or intramuscularly every third day, preceded on each occasion by the administration of four tablets (30 grains or 2g) of ammonium chloride by mouth two hours before. During the ambulatory stage the patient should take neptal tablets (three in all, or 0.48 Gm.), twice weekly in the more severe case, and once a week in the less severe case, after the same premedication, and receive an intravenous or intramuscular injection (2 c.c.) at intervals according to need.

AUTHORS.

Miller, J. R., and Van Dellen, T. R.: **Electrocardiographic Changes Following the Intravenous Administration of Magnesium Sulfate. III. Combined Effect With Digitalis.** J. Lab. Clin. Med. 26: 1116, 1941.

In the digitalized dog magnesium sulfate is capable of altering the contour of the T waves and producing a further delay in auriculoventricular conduction time in excess of that of digitalis or magnesium alone.

In the digitalized dog magnesium sulfate causes a brief increase in rate, followed by a slowing which approaches that obtained by digitalis. It is thus capable of overcoming the vagal stimulation produced by digitalis but for short periods only.

In the digitalized dog magnesium sulfate is capable of producing impulses of ectopic origin.

The results indicate that magnesium sulfate does not overcome the effects of digitalis intoxication but increases the degree of block and the occurrence of ectopic impulses.

AUTHORS.

Iglauer, A., and Altschule, M. D.: The Effect of Arterial and Venous Constriction Induced by Paredrine (p-Hydroxy- α -Methylphenylethylamine Hydrobromide) on the Lung Capacity and Its Subdivisions. *Am. J. M. Sc.* 201: 664, 1941.

The subdivisions of the pulmonary volume were measured in seven experiments on five normal subjects after the administration of paredrine.

No significant deviation from the control values occurred.

Paredrine therefore does not produce marked changes in the blood content of the capillaries of the lungs.

AUTHORS.

Hueper, W. C., and Ichniowski, C. T.: Experimental Studies in Cardiovascular Pathology. II. Pathologic Lesions in Organs of Cats, Guinea Pigs, and Frogs, Produced by Digitalis Poisoning. *J. Lab. and Clin. Med.* 26: 1565, 1941.

The introduction of single lethal doses of digitalis glycosides into guinea pigs, as well as of repeated sublethal doses of the drug into cats, results in the production of degenerative and necrotic myocardial and extracardiac (cerebral, suprarenal, hepatic, renal) organic lesions in the majority of the animals treated.

Some of the animals, however, dying from the toxic effects of the digitalis glycosides show at death no appreciable, or only minor cardiac, changes, while the extracardiac, and particularly cerebral, lesions are well developed.

The anatomic evidence obtained indicates that subacute and delayed death from digitalis poisoning may be the result of anatomic, myocardial lesions of severe type or, in the absence of these, of extracardiac cerebral or suprarenal lesions.

AUTHORS.

Modell, W., Gold, H., and Rothendler, H. H.: Use of Digitalis to Prevent Exaggerated Acceleration of the Heart. During Physical Exercise in Patients With Auricular Fibrillation. *J. A. M. A.* 116: 2241, 1941.

The average patient with auricular fibrillation has acceleration of ventricular rate during exercise chiefly, if not entirely, by decrease of the vagal tone. In these cases blocking the vagus by means of atropine accelerates the ventricles to the same maximum level as extreme physical exertion.

There is an indication that in some patients, especially those with advanced heart failure, an accessory mechanism for acceleration may also be invoked during extreme physical effort.

Exaggerated acceleration of the ventricles caused by physical exercise in patients with auricular fibrillation can be prevented in most cases by "extravagal" digitalization, a state in which the ventricles are slowed chiefly by the direct action of digitalis on auriculoventricular conduction and in which vagal tone has been, for the most part, lost. It is produced by relatively large doses of digitalis. In this state, the ventricular rate rarely exceeds 100 beats a minute after the vagi are blocked by atropine or after severe physical exercise.

The rate of the ventricles during rest does not disclose whether the digitalis has caused the slowing by the "vagal" or by the "extravagal" mechanism. There are two methods for determining "extravagal" digitalization: 1. the atropine test (the intravenous injection of 2 mg. of atropine sulfate) and 2. physical exercise. After neither of these tests will the ventricular rate rise appreciably above 100 beats a minute if enough digitalis has been given to cause slowing by the extravagal mechanism.

AUTHORS.

Book Reviews

THE HEART IN PREGNANCY AND THE CHILDBEARING AGE: By Burton E. Hamilton, M.D., Cardiologist to the Boston Lying-In Hospital, and K. Jefferson Thomson, M.D., Associate Physician, Metropolitan Life Insurance Co. Sanatorium, Mt. McGregor, New York, 1941, Little, Brown, and Co., Boston, 402 pages. \$5.00.

This book is important both to cardiologists and obstetricians. It contains the observations of a careful physician who has been seeing and treating cardiac patients during pregnancy over a period of twenty years. Many interesting statistical studies of various aspects of this series of 850 cardiac patients are presented, although at times the deductions from the statistics do not appear conclusive because other interpretations seem to be equally reasonable. Much of the material has appeared in the authors' previous publications, but it is here collected and discussed at length.

The book is divided into three separate parts. The first part considers the diagnosis of heart disease in pregnancy; this is followed by Hamilton's conclusions as to prognosis and treatment, based upon his experiences at the Boston Lying-In Hospital.

Much space is given to a description of the diagnostic features of valvular disease, but too little space is devoted to a definition of the diagnosis of heart failure. It is not made clear at what stage of the process of cardiac insufficiency the authors would begin to apply the term "heart failure." Certain writers restrict this term to a condition associated with marked limitation of physical activity due to cardiac symptoms and associated with certain physical signs. That the authors do not have this condition in mind is apparent from the statement that "persistent râles are typically an early and sometimes subclinical sign of heart failure, appearing before the patient notices any change in her breathing." A history of heart failure, as related by the patient, must certainly depend upon a more marked degree of failure than this, so that the patient's history of heart failure and the demonstration of heart failure in the authors' clinic must obviously represent quite different degrees of the process. It does not seem, for this reason, that "the finding of a history or of signs of heart failure" should be used interchangeably as a basis for placing a woman in the class of "unfavorable" cardiacs.

Nevertheless, the method suggested for dividing cardiacs as to prognosis must have definite value because of the great difference in the mortality statistics between the "favorable" and "unfavorable" groups of patients with heart disease. Hamilton's statement that "any cardiac may fail at any time" suggests, however, that in his experience this method of dividing cardiacs does not serve to separate those who may develop failure from those who will not. It is the experience of most of those who have used the New York Heart Association classification that such a grouping is found in the patients with Class I Functional Capacity, and yet the authors see no value for prognosis in dividing cardiacs on the basis of functional capacity, as outlined by the New York Heart Association. Others, however, have found this method of value, and the final decision as to its usefulness must await further experience.

Hamilton obtains no assistance from observation of the patient after an effort test, and considers this "too harsh a method for estimating the state of delicate cardiacs in pregnancy." This seems to ignore the evident fact that there are

some cardiacs who are not delicate during pregnancy, and are able to carry on their accustomed household tasks, perhaps in addition to taking care of a numerous and troublesome family of children.

There are interesting observations on the influence of age and parity upon the prognosis of heart disease during pregnancy, and on the influence exerted by auricular fibrillation and other arrhythmias, and by serious complicating diseases, such as tuberculosis, syphilis, hypertension, pre-eclampsia and eclampsia, and pyelitis, upon the course of cardiac patients. The observation that heart failure seldom occurs for the first time at or following delivery has far-reaching implications which are developed in detail. Seventy-five per cent of the deaths, however, occurred during the puerperium, and 25 per cent occurred during pregnancy.

There is an important and practical discussion of the factors which may precipitate or contribute to heart failure, under the headings of infection, fatigue, gain in weight, anemia, and other less important and less frequent conditions. Also of great practical importance is the regime for the prevention of congestive heart failure. It is a detailed discussion of the directions to be given to the pregnant patient with cardiac disease in order to lessen the chance that she might develop heart failure. If we believe, as do the authors, that under a sufficiently severe strain "any patient with mitral stenosis may develop congestive failure suddenly, no matter how favorable the particular case may appear," then these restrictions must be applied to all cardiacs, as they recommend. Many cardiologists might feel that a weekly visit is more of a luxury than a necessity for many patients, but the authors do not believe so. They feel that it is particularly important from the end of the fifth to the end of the eighth month, a dictum in which all would join. By this close observation they have noted the development of congestive heart failure in 20 per cent of all their cardiacs at some time during pregnancy.

There is a very common-sense and realistic section on the part the physician should play in advising against pregnancy or in advising therapeutic abortion because of heart disease. Hamilton believes that it is not the physician's part to recommend, but that he should give his patient the benefit of his knowledge of the degree of risk involved in a case such as hers, and so help her to a decision as to the course she would desire to pursue.

There is an excellent chapter by Dr. F. C. Irving, on the principles and methods used for delivery of cardiacs at the Boston Lying-In Hospital. His observations on the features which favor abdominal section, as against induced labor, in the third to sixth month, on the desirability of avoiding hysterotomy in the later months, and of avoiding vaginal hysterotomy at all times, deserve serious consideration.

In the aftercare of cardiacs, emphasis is placed upon avoiding the administration of excessive fluid to those who show signs of heart failure. The harmlessness of nursing the infant is also emphasized. The authors' statistics on the rate of fetal mortality in this group of cases show a surprisingly high figure, even in the group of "favorable" cardiacs. To the knowledge of the reviewer, this has not before been prominently mentioned.

The second part of the book contains an important series of observations upon the variations of various circulatory functions during normal pregnancy, and the modifications of these functions that result from cardiac disease. Observations on the symptoms and clinical examination of a group of normal pregnant women are followed by observations on the heart size, as shown roentgenologically, the electrocardiogram, roentgenologic studies of the lungs and thorax, the vital capacity, the pulse and respiratory rate, the arterial pressure, venous pressure, circulation time, blood volume, and other features. Similar observations on a group of 99 pregnant cardiacs show the importance of vital capacity observation as an aid in the diagnosis of heart failure, and the possible usefulness of a measurement of total blood volume.

Book Three returns to the clinical aspects of heart disease in pregnancy, but particularly in women of the childbearing age who are not pregnant. The effects upon cardiacs of complicating diseases such as eclampsia, hypertension, and recurrent rheumatic fever are discussed, and also the effect of various valve lesions upon the prognosis. Congenital heart disease is discussed as it is observed in young women of the childbearing age, and the effects upon these patients of pregnancy and labor are pointed out.

This volume is an interesting exposition of Hamilton's conclusions from his experiences at the Boston Lying-In Hospital. It represents an important contribution to our knowledge of a small, and perhaps somewhat neglected, phase of cardiac disease.

HAROLD E. B. PARDEE.

ELEKTROKARDIOGRAPHIE FÜR DIE ÄRZTLICHE PRAXIS: By Prof. Dr. Erich Boden, Düsseldorf. Sechste Auflage, Band 14, Medizinische Praxis, 1941, Theodor Steinkopff, Dresden, 194 pages, 107 illustrations, R.M. 7.50.

This book is one of a set of twenty-nine volumes covering a wide range of both medical and surgical subjects, and was designed primarily for the general practitioner. It is a series of fifteen lectures—five on the theoretical and experimental aspects of electrocardiography, and ten on its practical application. The text is concise, and the illustrations are well chosen and beautifully executed. The volume quite adequately fulfills the purpose for which it was designed.

ROY W. SCOTT.

THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE: By fifty-six contributors, edited by William D. Stroud, M.D., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine, F. A. Davis Co., Philadelphia, 1940, 2 volumes, 1825 pages, 400 illustrations, \$18.00.

These two volumes are the most monumental work that has yet appeared in the field of cardiovascular disease, and represent the cooperative endeavors of fifty-six well-known American authorities who are eminently qualified as clinicians, and, for the most part, as investigators of the subjects with which they deal. Few appraisals of the work will carry more weight than that given in the foreword by Sir Thomas Lewis, who writes: "The brilliant list of American authors of the present contents includes a score of names known in every part of the world where cardiovascular diseases have been intensively studied; they are known for the solid contribution of those who bear them to their subject. Rarely before have such a number of authoritative writers combined to place its views of a branch of medicine on record, and never before of cardiovascular disease; it is a guarantee to the reader that he is in direct or close contact with all the fountains of modern knowledge, the most important guarantee perhaps that any reader can be given."

Even if space permitted, the reviewer is not qualified to make a critical survey of each contribution in these volumes. Therefore, with a few exceptions, little more than an enumeration of the various subjects which are presented will be attempted, but even this will give the reader an idea of the scope of the work.

The introductory chapter, contributed by Sprague and White, deals in an able way with the classification of cardiovascular diagnosis. Since a correct diagnosis is the first step in sound therapy, a careful survey of the patient is imperative, and experience has taught that, in the field of cardiovascular disease, this is best accomplished by considering in each case (1) the etiologic factor or factors responsible for the disease, (2) the resulting anatomic changes in the heart and vessels, (3) the functional disturbances which are known to occur, and (4) the immediate or ultimate effect of the disease on the patient's ability to carry on. Under these four headings the authors list the various conditions which are observed clinically and at autopsy in cases of cardiovascular disease.

There follows a chapter on congenital cardiac abnormalities which needs no further commendation than to state that it was written by the late Maude E. Abbott, whose extensive and scholarly work in this field is known the world over. Rheumatic fever is discussed in three chapters; one is by McEwen, who presents, in a comprehensive way, rheumatic heart disease, with illustrative case reports; another, by Paul, is on the epidemiology; and a third is by Jones, who deals with a most important aspect of the subject, namely, evaluation of active infection. Whether a patient has an initial attack of rheumatic fever, a recrudescence of an earlier attack, or some other disease, is often a difficult diagnostic problem. Both clinical and laboratory evidences of active rheumatic infection are discussed by Jones.

A chapter on bacterial endocarditis, by Dock, is good as far as it goes, but too little attention is paid to the discussion of that most important type of endocarditis, namely, subacute bacterial endocarditis, which is usually caused by the implantation of the *Streptococcus viridans* on a scarred or congenitally deformed endocardium. An additional chapter covering this important subject would have enhanced the value of the treatise.

A sound, well-written chapter on cardiovascular syphilis is contributed by Paullin and Minnich, who rightly emphasize that syphilis is an important cause of heart disease only insofar as it involves the root of the aorta, and thereby leads to aortic insufficiency, dilatation of the aortic ring, or occlusion of coronary ostia. Stokes and Anderson cover the treatment of cardiovascular syphilis in a concise and adequate fashion. A chapter on the heart in hyperthyroidism is contributed by Thomas. At this point there might well have been a discussion of the myxedema heart, and why it was omitted is not clear. Conner writes on cardiac neurosis; Porter, on the heart in anemia; and Durant, on cor pulmonale. In a chapter entitled "The Cardiovascular System With Relation to the Kidneys," Hayman discusses the effect of hypertension on the heart and gives the best presentation of the problem of essential hypertension, in the light of recent experimental work, that is contained in the book.

A chapter on the heart in diseases of the glands of internal secretion was written by Barr, and cardiac trauma is handled by Barber. Porter has a chapter on acute pericarditis, and White one on chronic constrictive pericarditis. Roesler contributes a chapter on cardiac hypertrophy and dilatation, and Vander Veer one on chronic valvular heart disease. A clear presentation of coronary artery disease is given by Smith, and Levy writes on the diagnosis of coronary insufficiency, based largely on his experience with the anoxemia test. Stroud also writes a chapter on coronary disease; his remarks on treatment are notably sound and might well have been extended. A short chapter on nourishment of the heart by channels other than the coronary arteries was written by Bellet; the normal heart is discussed by King, and Levine writes on the cardiac patient as a surgical risk. Noteworthy for its lucidity and excellent illustrations is a chapter on heart sounds, by Wolferth and Margolies.

Done with characteristic thoroughness is a chapter on the form of the electrocardiogram, by Wilson, who is concerned with the cause and significance of the various deflections in the electrocardiogram, both normal and pathologic. There follows a well illustrated chapter by Bellet and McMillan on clinical electrocardiography, covering the clinical disorders of the heart beat, myocardial infarction, and other conditions resulting in abnormal electrocardiograms. The roentgenology of the heart and vessels is treated by Margolies, and the final chapter of Volume One, on disturbances of the heart beat, was written by Herrmann.

The first 318 pages of Volume 2 deal with various aspects of heart disease, and here we find several chapters on the general management of the cardiac patient. Stroud and Vander Veer write on the clinical efficacy of various digitalis preparations; Stroud writes on the cardiac patient in industry; Beck, on surgery of the heart and pericardium; Grant, on relief of pain in angina pectoris by paravertebral

sympathetic block with alcohol; Kerr, on the use of quinidine in cardiac irregularities; Blumgart and Riseman write on total thyroidectomy in the treatment of chronic heart disease, and Comstock and Stroud on physical therapy in cardiovascular disease. Marvin contributes an interesting chapter on the prevention and relief of heart disease as a public health problem, and points out that until we have more fundamental knowledge of human arteriosclerosis, we can speak with no assurance regarding the prevention of such common types of heart failure as hypertensive heart disease and coronary artery disease. Marvin also gives a review of the origin and aims of the American Heart Association, which is the one national organization concerned with all aspects of the problem of cardiovascular disease.

Bromer and Stroud write a chapter on congestive heart failure and one on left ventricular failure which review the modern concepts concerning pathogenesis and outline the management of the conditions. A chapter on the effects of digitalis on the electrocardiogram is contributed by McMillan, and Bellet and Weiss write on the heart and deficiency diseases.

The remaining 505 pages of Volume Two are devoted to peripheral vascular disease, starting with a comprehensive chapter by Allen on normal blood pressure and its variations. There follow a chapter on capillary circulation by DeGraff and Koffmann, and one on shock by Freeman.

Stieglitz writes a chapter on hypertensive arterial disease which conveys a somewhat obsolete view of the subject, in the light of the more recent experimental work of Goldblatt and his associates, which has demonstrated the role of the kidney in the etiology of arterial hypertension. Stieglitz' discussion of the subject is colored by his views on the pathogenesis of hypertension associated with arteriolar sclerosis, and is best summarized by quoting him verbatim: "What starts out as a purely physiological response becomes a progressive and destructive disease," and, elsewhere, "the anatomic physiologic changes of hypertensive arterial disease are the result rather than the cause of hypertension." Such categorical statements cannot be defended, since there is at present strong evidence in support of the view that arteriolar disease of the kidney, leading to renal ischemia, is the cause rather than the result of hypertension. Stieglitz tabulates a long list of predisposing and provoking factors which cause peripheral vascular spasm, and believes that, as the result of long continued hypertension, there follow, in order, first, hypertrophy, then degeneration, and, finally, fibrosis of the media, which he considers the essential lesions of arteriolar sclerosis. By most authorities, simple arteriosclerosis is regarded as primarily an intimal disease even when it affects the arterioles. In his discussion of the treatment of hypertension, Stieglitz makes no mention of hypertension associated with unilateral kidney disease. The logical and already successful treatment by excision of the diseased kidney in many cases is well known, and certainly merits consideration in any current discussion of hypertension.

In a chapter on psychic factors in arterial hypertension, Houston discusses the well-known effect of psychogenic factors on blood pressure levels, but, after reading the chapter, one feels that undue emphasis is placed on the role of the nervous system in causing hypertension and vascular disease. He, like Stieglitz, believes that the chief factor leading to arteriolar disease is hypertension, but unfortunately the problem of human arteriosclerosis is not so simple. For example, careful clinical and post-mortem studies show that negroes have more hypertension than whites, yet significantly less coronary artery disease. If hypertension were the major cause of vascular disease, obviously the negro should have more coronary disease than the white man. If worry and the strain of living were so important as Houston believes, it is indeed difficult to explain the fact that negroes, even in the deep South, have more hypertension than whites.

Barach writes a chapter on low arterial pressure which is eminently sound. He rightly emphasizes the fact that, in the absence of active disease, persons with low arterial pressures live longer than those with normal or high blood pressure.

Moschcowitz has a chapter entitled "Arteriosclerosis" which outlines the well-known pathologic changes, with remarks on pathogenesis, incidence, and localization of the affection, but in his discussion of the etiology of arteriosclerosis he is "groping in the dark for something in the dark." He would have us believe that hypertension is the sole cause of arteriosclerosis, according to the simple equation: arteriosclerosis = intravascular pressure \times time. In his zeal to prove this thesis, he exhibits a wanton disregard for the old observation that (1) many elderly people with extensive and severe arteriosclerosis never had hypertension, and (2) that many middle-aged patients with coronary and cerebral artery sclerosis have a normal blood pressure. Would that the etiology of human arteriosclerosis were as simple as Moschcowitz claims! Considering the importance of the subject, his presentation of it leaves much to be desired.

A terse and adequate account of periarteritis nodosa is written by Farley, and a chapter on thromboangiitis obliterans is contributed by Buerger, whose extensive experience with this affection is plainly evident. A discussion of erythromalgia (erythromelalgia) of the extremities, lymphedema of the extremities, and sudden embolism and thrombosis of arteries of the extremities is adequately presented by Allen. Thrombophlebitis is handled by Barker, and acquired arteriovenous fistula, temporal arteritis, and aneurysm, by Hines. A sound and well-illustrated chapter on arteriosclerosis obliterans is written by Wright, who recognizes the nature of the problem, and, avoiding dogmatic assertions regarding the etiology, gives the reader a comprehensive account of the subject. Wright also contributes a chapter on Raynaud's syndrome and acrocyanosis, with colored illustrations that are outstanding. De Takats writes a chapter on vascular anomalies, and also one on varicose veins; both are well illustrated and adequately cover the subject. Volume Two closes with a scholarly discussion of the pathogenesis and treatment of edema, by Landis.

This treatise has the merits, as well as the disadvantages, which are inherent in a work by many authors. One finds considerable reduplication, which might be deleted; and a better arrangement of sequence of the chapters would considerably enhance the value of the book.

The various authors have made good use of illustrations and case reports, and the treatise has an excellent index. For the beginner, as well as for the physician who knows cardiovascular disease, but wants to know it better, this work has much to commend it.

ROY W. SCOTT.

NATURHEILKUNDLICHE BEHANDLUNG VON HERZKRANKHEITEN; ELEKTROKARDIOGRAPHISCHE STUDIEN: By Dr. Med et Phil. Franz Kienle, Assistant an der medizinischen Klinik der Rudolf Hess Krankenhaus, Dresden. Theodor Steinkopff, Dresden, 1940, 155 pages, 145 illustrations.

The author attempts to prove in this short monograph that nature healing is more effective in controlling myocardial failure and disturbances in heart rhythm than conventional therapy. The nature treatment consists of a liquid diet, followed by a soft diet, and later raw vegetables. Physical treatment consists of massage, warm arm- and foot-baths, carbonic acid baths in selected cases, and bandaging of the chest. In the introduction by Grote, credit is given to the late Reichs-ärztführer, Dr. Gerhard Wagner, for the advocacy of the method. Electrocardiographic studies before and after treatment are presented in an attempt to prove the curative results. Only one case was reported in which there was failure of the method. Cases of myocardial failure of all types, extrasystoles, paroxysmal tachycardia, true and false bundle branch block, and heart block are reported. In his conclusion, Kienle states that nature healing will in great measure meet all requirements, and only rarely will it be necessary to introduce medical treatment.

The electrocardiographic interpretation is fanciful at times, especially when the author presents it as evidence of improvement.

The book can be recommended only as evidence that there is a new school of thought in Germany, wherein old and tested methods of therapy are scrapped in favor of *naturheilkundliche Behandlung*.

HAROLD FEIL.

HERZKRANKHEITEN, BAND 1: PHYSIOLOGIE, BEURTEILUNG, UND FUNKTIONELLE PATHOLOGIE DES HERZENS: By Prof. Dr. Max Hochrein, Direktor der Medizin, Universitäts Poliklinik, Leipzig. Theodor Steinkopff, Dresden and Leipzig, 1941, 480 pages, 170 illustrations.

This is a good exposition of diseases of the heart, chiefly from a physiologic point of view. The review includes many of the newer conceptions and is fairly comprehensive. Opening with a recapitulation of normal anatomy and physiology, Hochrein continues with clinical aspects, then follows with a full discussion of the pathologic physiology of diseases of the circulation. It is a sound work. The author presents to the German medical profession the currently accepted ideas about heart disease, including much English and American work.

HAROLD FEIL.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. PAUL D. WHITE
President

DR. ROY W. SCOTT
Vice-President

DR. T. HOMER COFFEN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

*DR. EDGAR V. ALLEN	Rochester, Minn.	*DR. EDWIN P. MAYNARD, JR.	Brooklyn
DR. T. HOMER COFFEN	Portland, Ore.	*DR. THOMAS M. MCMILLAN	Philadelphia
DR. CLARENCE DE LA CHAPELLE	New York City	DR. JONATHAN MEAKINS	Montreal
DR. WILLIAM DOCK	San Francisco	DR. E. STERLING NICHOL	Miami
DR. HUGH FARRIS, St. John, N. B.,	Canada	DR. FRANKLIN R. NUZUM	Santa Barbara
DR. NORMAN E. FREEMAN	Philadelphia	*DR. STEWART R. ROBERTS	Atlanta
DR. GEORGE R. HERRMANN	Galveston	*DR. ROY W. SCOTT	Cleveland
DR. T. DUCKETT JONES	Boston	DR. FRED M. SMITH	Iowa City
*DR. WILLIAM J. KERR	San Francisco	*DR. HOWARD B. SPRAGUE	Boston
DR. EMANUEL LIBMAN	New York City	DR. WILLIAM D. STROUD	Philadelphia
DR. DREW LUTEN	St. Louis	*DR. PAUL D. WHITE	Boston
DR. GILBERT MARQUARDT	Chicago	DR. FRANK N. WILSON	Ann Arbor
*DR. H. M. MARVIN	New Haven	*DR. IRVING S. WRIGHT	New York City
		DR. WALLACE M. YATER	Washington, D. C.

DR. H. M. MARVIN, *Chairman, Executive Committee
and Acting Executive Secretary*

GERTRUDE P. WOOD, *Office Secretary*

TELEPHONE CIRCLE 5-8000

THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-seven physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$11.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

•Executive Committee.

The American Heart Journal

VOL. 22

OCTOBER, 1941

No. 4

Original Communications

RHEUMATIC INFECTION IN CHILDHOOD: INFLUENCE OF TYPE OF ONSET AND CALENDAR YEAR OF ONSET

RACHEL ASH, M.D.
PHILADELPHIA, PA.

IN A PREVIOUS paper¹ a statistical analysis was presented of a group of rheumatic patients who had been under the care of the Children's Hospital during the years 1922-1932, inclusive. The initial year, 1922, was chosen because it marked the time when the clinic for supervision of patients with rheumatic infection or heart disease had been founded by the late Dr. Horace H. Jenks.

The present paper extends this analysis to cover the first fifteen years of the clinic. It is based on a follow-up study of all rheumatic children whose primary manifestation had occurred during the years 1922-1936, inclusive, and who had come under the care of the Children's Hospital, either in the wards or Outpatient Department. Rheumatic infections of all degrees of severity were included. Forty-six children had been admitted to the ward with infection serious enough to result in death before the termination of the first year of the disease. In five instances the duration of the fatal illness had been less than one month. Seventy-eight children had been cared for solely through the Outpatient Department. Of the children discharged from the ward, those unable to afford private medical care had been kept under the supervision of the clinic until their fourteenth year, at which time they were transferred to cardiac clinics for the care of adults. Patients of private physicians were advised to remain under the continuous supervision of their medical advisors.

All children on whom the diagnosis of rheumatic infection had been made were included, irrespective of the presence or absence of clinically recognizable heart disease.

Of the original group of 583 children, 473 (81.1 per cent) were white; 110 (18.9 per cent) were colored; 255 (43.8 per cent) were

From the Children's Hospital of Philadelphia and the Department of Pediatrics, University of Pennsylvania Medical School.

Received for publication Feb. 14, 1941.

males, and 328 (56.2 per cent) were females. One hundred thirty-seven (23.8 per cent) had been under the care of the Children's Hospital prior to the onset of rheumatic infection.

The average age at onset was 6.9 years, with limits varying from 17 months to 12 years. Six children were less than 2 years of age at the time of their primary manifestation, and nineteen, less than 3 years.

In 1939, all children not under current observation were requested to return for examination. Additional information was obtained from the records of other hospitals or private physicians who at some time had been responsible for the care of these patients. As a result of these efforts, 527 (90.4 per cent) were traced. Of those concerning whom no information could be obtained in 1939, twenty-six had been followed previously for periods ranging from three to thirteen years. The course of the disease was thus known over a minimum period of three years and an average period of 9.6 years for 553 rheumatic children. Among these, signs of heart disease had been noted at one time or another in 414 (71.0 per cent), but, because of regression of such signs in some patients, a diagnosis of organic valvular damage had eventually been made in only 355 (64.2 per cent). One hundred forty-six (26.4 per cent) had died; of these, 120 (21.7 per cent) had died of rheumatic infection only; 13 (2.3 per cent) of superimposed bacterial endocarditis; 7 (1.3 per cent) with an associated infection, e.g., pulmonary tuberculosis, diphtheria, pertussis, scarlet fever, lobar pneumonia (three cases); and 6 (1.1 per cent) of unrelated causes (Table I).

TABLE I

TOTAL GROUP: PROGNOSIS ACCORDING TO DURATION OF RHEUMATIC INFECTION

DURATION YEARS	PATIENTS NO.	VALVULAR HRT. DIS. %	DEATHS		SURVIVORS		
			RHEU- MATIC %	BAC- TERIAL ENDO- CARDITIS NO.	PATIENTS NO.	VALVULAR HRT. DIS. %	POSSIBLE HRT. DIS. %
1	564	57.9	7.9	1	514	53.3	11.0
3	553	60.4	13.2	2	473	53.9	13.8
5	501	62.0	16.9	4	405	54.5	11.6
7	413	65.6	22.5	7	308	54.5	11.7
10	280	70.4	29.8	2	199	54.8	7.0
{3 to 17 Average 9.6	553	64.2	21.7	13	398	52.3	12.0

Nine patients were known to be leading a normal existence, but no information was available as to their cardiac status. At the final examination of the remaining 398 survivors, 208 (52.3 per cent) presented signs of organic valvular disease; in 48 (12 per cent), murmurs were audible which could not be differentiated from those of accidental or functional origin; 142 (35.7 per cent) showed no signs of heart damage. Twenty-two were ill with acute recurrences. Ten were cardiac

invalids. The remaining were leading a normal life, although thirty-seven were slightly limited in their ability to undertake physical exertion. Of the twenty girls who had married, all were doing their own housework. Ten had given birth to fifteen children.

The criteria used for diagnosis were those advocated by the American Heart Association.² For the detection of cardiac enlargement, use was made only of the position of the apex beat and the teleroentgenograms. No application was made of the angle of clearance test described by Wilson.³

INFLUENCE OF THE TYPE OF ONSET ON PROGNOSIS

Since the course of rheumatic infection is modified by many variable factors, analysis of a heterogeneous group over an average period of time may be misleading. In an attempt to obtain further information, the course of the disease as modified by the type of initial infection has been traced over definite periods of time.

In considering the initial infection, antecedent upper respiratory infections, including pharyngitis and tonsillitis, have been ignored, because, in the present state of our knowledge, it does not seem possible to decide whether such infections are coincidental, predisposing, or true primary manifestations.

TYPE OF ONSET

Acute carditis (47 children; 8 per cent).—The diagnosis of primary carditis was made in the presence of a febrile illness of sudden onset, associated with signs of cardiac damage. Sudden primary carditis tended to attack the youngest children, for the average age at onset (5.7 years) was somewhat over a year less than that of the group as a whole (6.9 years). The initial mortality was highest among these children, 30 per cent of whom ran a rapidly fatal course, and 65 per cent of whom were dead at the end of ten years. Regression of signs of heart disease occurred in only two instances (Table II).

TABLE II
ONSET WITH ACUTE CARDITIS: PROGNOSIS ACCORDING TO DURATION OF
RHEUMATIC INFECTION

DURATION YEARS	PATIENTS NO.	VALVULAR HRT. DIS. %	DEATHS		SURVIVORS		
			RHEU- MATIC %	BAC- TERIAL ENDO- CARDITIS NO.	PATIENTS NO.	VALVULAR HRT. DIS. %	POSSIBLE HRT. DIS. %
1	46	97.8	30.4	0	32	96.9	0
3	45	97.8	42.2	0	26	96.1	0
5	40	95.0	45.0	1	21	90.5	4.8
7	31	96.8	51.6	1	14	92.9	0
10	23	100.0	65.2	1	7	100.0	0

Polyarthrititis (314 children; 53.9 per cent).—The diagnosis of acute polyarthrititis was made when the initial illness was associated with migratory joint pains, fever, and prostration of a degree sufficient to require rest in bed. The average age at onset (6.6 years) was only slightly less than that of the group as a whole. The incidence of clinically demonstrable heart disease at the onset was 59 per cent. Of the patients whose illness had run a course of ten years, 72 per cent suffered from rheumatic heart disease. Almost 10 per cent of the children were dead at the end of the first year, and 30 per cent, at the end of ten years (Table III). It was, however, among the children with early cardiac damage, the extent of which increased with each recurrence, that death occurred most frequently. In contradistinction, of thirty-four children with an early diagnosis of potential or possible heart disease who had been traced at the end of ten years, only 24 per cent had developed definite heart disease, and death had occurred in only one instance.

TABLE III

ONSET WITH ACUTE POLYARTHRITIS: PROGNOSIS ACCORDING TO DURATION OF RHEUMATIC INFECTION

DURATION YEARS	PATIENTS NO.	VALVULAR HRT. DIS. %	DEATHS		SURVIVORS		
			RHEU- MATIC %	BAC- TERIAL ENDO- CARDITIS NO.	PATIENTS NO.	VALVULAR HRT. DIS. %	POSSIBLE HRT. DIS. %
1	301	59.1	9.6	0	270	53.5	12.6
3	297	63.6	16.1	0	246	56.1	13.0
5	264	65.5	19.7	1	218	54.5	10.5
7	224	67.0	25.0	4	163	54.6	11.6
10	151	72.4	30.4	4	100	59.0	7.0

Chorea (116 children; 19.8 per cent).—The diagnosis of Sydenham's chorea was made only in the presence of the triad of emotionalism, hypotonia of muscles, and gross incoordinate movements of an abnormal nature. Chorea tended to attack the older children; the average age at onset (8.0 years) was approximately one year greater than that of the group as a whole. In itself, it was a relatively benign manifestation. At the end of the first year, 22 per cent had valvular heart dis-

TABLE IV

ONSET WITH CHOREA: PROGNOSIS ACCORDING TO DURATION OF RHEUMATIC INFECTION

DURATION YEARS	PATIENTS NO.	VALVULAR HRT. DIS. %	DEATHS		SURVIVORS		
			RHEU- MATIC %	BAC- TERIAL ENDO- CARDITIS NO.	PATIENTS NO.	VALVULAR HRT. DIS. %	POSSIBLE HRT. DIS. %
1	113	21.6	2.7	0	108	19.5	5.5
3	110	31.9	2.8	0	106	30.2	11.3
5	101	38.6	3.9	1	94	37.2	11.7
7	81	44.0	9.9	0	71	38.0	14.1
10	56	41.0	16.1	1	46	39.1	6.5

case, and 2.7 per cent had died. After ten years, 41 per cent suffered from rheumatic heart disease, and 16 per cent were dead (Table IV). All deaths had resulted from carditis, which had made its appearance subsequent to onset. In only nine of the forty-six cases of rheumatic heart disease had the latter developed without a known history of arthritis, carditis, or myalgia. The diastolic rumble of mitral stenosis became suddenly audible in two patients whose only previous rheumatic manifestation had been chorea.

Myalgia and joint pains (53 children; 9.6 per cent).—Children with complaints of myalgia and joint pains not severe enough to force them to go to bed were considered rheumatic if such pains were associated with signs of infection, such as increased sedimentation rate, leucocytosis, or slight fever. Many were brothers or sisters of patients who had suffered from more acute manifestations. These children tended to be older than the run of the group; the average age at onset was 7.5 years. Heart disease at onset was noted in 47 per cent, and at the end of ten years in 58 per cent, at which time 17 per cent were dead (Table V).

TABLE V

ONSET WITH MYALGIA AND JOINT PAINS: PROGNOSIS ACCORDING TO DURATION OF RHEUMATIC INFECTION

DURATION YEARS	PATIENTS NO.	VALVULAR HRT. DIS. %	DEATHS		SURVIVORS		
			RHEU- MATIC %	BAC- TERIAL ENDO- CARDITIS NO.	PATIENTS NO.	VALVULAR HRT. DIS. %	POSSIBLE HRT. DIS. %
1	55	47.3	0	0	55	47.3	25.4
3	53	41.5	3.7	0	50	38.0	30.0
5	50	40.0	8.0	0	45	33.3	20.0
7	35	54.3	8.6	0	31	48.4	33.3
10	24	58.3	17.0	0	20	50.0	15.0

Insidious Carditis (48 children; 8.7 per cent).—A diagnosis of insidious carditis was made when valvular lesions characteristic of rheumatic heart disease were found on the first examination of a child with no known history of illness or with a history of scarcely recognized,

TABLE VI

ONSET WITH INSIDIOUS CARDITIS: PROGNOSIS ACCORDING TO DURATION OF RHEUMATIC INFECTION

DURATION YEARS	PATIENTS NO.	VALVULAR HRT. DIS. %	DEATHS		SURVIVORS		
			RHEU- MATIC %	BAC- TERIAL ENDO- CARDITIS NO.	PATIENTS NO.	VALVULAR HRT. DIS. %	POSSIBLE HRT. DIS. %
1	49	100	0	0	48	95.8	4.2
3	48	93.6	2.1	2	44	95.4	4.6
5	46	89.1	14.6	0	37	89.2	10.8
7	39	92.3	25.6	1	26	88.4	11.6
10	26	96.1	37.0	0	16	93.7	6.3

mild symptoms of ill-health. When no definite information as to initial illness could be elicited, the time of the first examination was taken as the time of onset. The average age of this group when the state of ill-health was first noted was 7.0 years. At the end of ten years 37 per cent were dead (Table VI).

INFLUENCE OF CALENDAR YEAR OF ONSET ON PROGNOSIS

The previous follow-up study of patients who were seen prior to 1932 had presented evidence to indicate a progressive lessening of severity of rheumatic infection. The present analysis shows a continuation of this trend. In each successive five-year period since 1922, there has been a lowering of mortality and of the incidence of obvious cardiac involvement, both in the entire group and among those whose first manifestation was polyarthritis or acute carditis (Fig. 1).

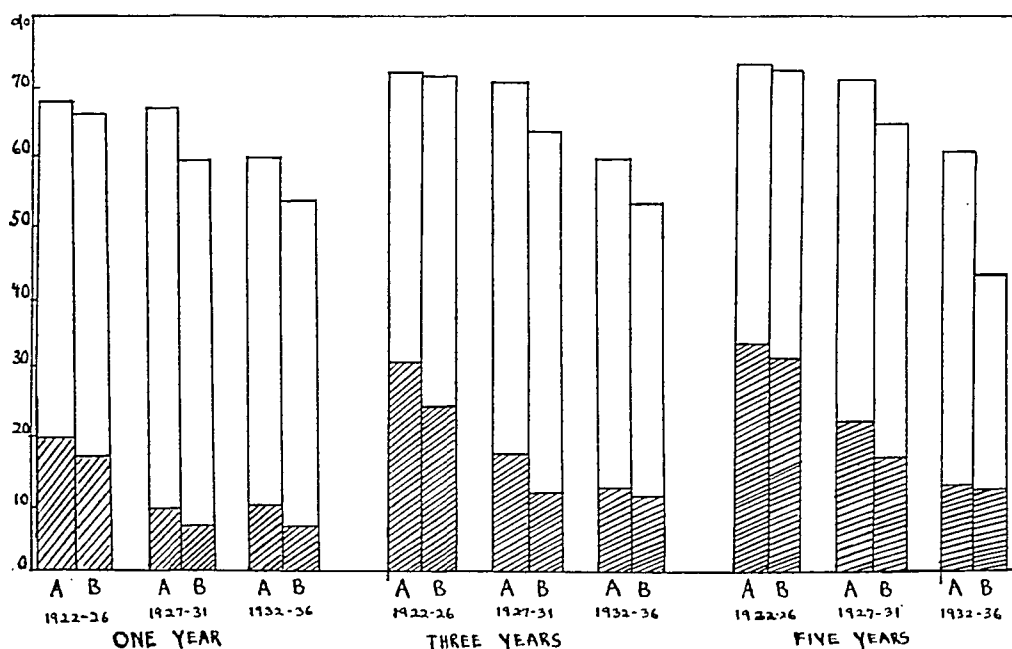


Fig. 1.—Trend toward lessening of severity of rheumatic infection over fifteen-year period. Column A indicates the incidence of cardiac involvement in the entire group, with onset of infection during the years noted, and Column B, the incidence among those with polyarthritis or carditis at onset. The shaded areas indicate the percentage of deaths due to rheumatic infection.

Various factors have been analyzed in the effort to find out whether this seeming improvement might have been due to a difference in the composition or treatment of the group.

There has been a shift in racial composition during the period of observation; the number of colored children has shown a slow increase, whereas, among the white patients, children of Italian derivation have increased in number (Table VII). Such a change, however, should have influenced the situation for the worse, because the death rate among colored children was 31 per cent, as compared with a death rate of 22 per cent among Italian children and 22.5 per cent among all white children.

TABLE VII
RACIAL COMPOSITION

YEARS OF ONSET	WHITE		BLACK		ITALIAN %	HEBREW %	NORTH EUROPEAN %
	#	%	NO.	%			
1922-1926	127	85.8	21	14.2	35.8	12.2	37.8
1927-1931	170	81.7	38	18.3	44.2	6.7	30.8
1932-1936	153	77.3	45	22.7	50.5	5.6	20.4

The distribution of children according to type of onset shows no significant variation within each of these five-year periods. The incidence of cardiac damage of sufficient severity to present obvious clinical signs has, however, shown a progressive decline among children whose first manifestations were those involving the joints (Table VIII).

TABLE VIII
DISTRIBUTION ACCORDING TO TYPE OF ONSET

	1922-26		1927-31		1932-36	
	PER CENT OF TOTAL GROUP	INCIDENCE OF CARDITIS FIRST YEAR	PER CENT TOTAL GR.	INCIDENCE CARDITIS FIRST YR.	PER CENT TOTAL GR.	INCIDENCE CARDITIS FIRST YR.
Polyarthritis or joint pains	63.4	70.2	64.7	64.2	62.2	52.0
Chorea	18.2	22.2	18.8	25.6	21.7	21.4
Carditis, acute or insidious	18.2	100.0	16.4	100.0	16.1	100.0

There has been no consistent decrease in recurrences within the first three years after onset. Among those taken ill in 1922-26, 68 per cent suffered recurrent attacks of polyarthritis, carditis, chorea, or joint and muscle pains of rheumatic origin within three years. Among those attacked during 1926-31, the percentage of recurrences had risen to 75. The year 1929, which fell during this period, had previously revealed itself as a year in which rheumatic manifestations were unduly frequent. The early years of the depression, beginning with 1929, were difficult years for many of the families cared for at the Children's Hospital; there was sudden unemployment at a time when no consistent policy of organized relief had been established. Despite the increase in recurrences, however, the death rate continued to decline. In the third five-year period, recurrences within the first three years had dropped to 56 per cent. In the entire group, 64.3 per cent developed recurrences within three years, and 70.5 per cent within five years. Nine per cent were free from rheumatic manifestations for a period of five years after the original attack, only to develop a flare-up of the disease subsequently.

The policy of the hospital regarding admissions has not changed. To what, then, may we attribute the improvement in the clinical course?

Part, if not all, of this improvement would seem to be due to a spontaneous change in the character of the disease. Hedley⁴ has re-

cently brought to our attention the decrease in mortality from heart disease since 1922 among persons between 5 and 24 years of age, a period when rheumatism is the most frequent etiologic factor. In the Middle Atlantic States, the decline in the mean death rate during 1930-36, as compared with 1922-29, was 27.2 per cent, and, in Pennsylvania, 24.5 per cent. At the Children's Hospital the death rate during the first three years among children who were taken ill during 1930-36 was 10.8 per cent, as compared with 18.3 per cent among those taken ill during 1922-29, a decline of 40.9 per cent.

Although there has been no change of policy regarding admissions at the Children's Hospital, it is perhaps significant that within recent years there has been a change in the relative attention paid to the child with the first manifestation of the disease. Prolongation of hospital stay, moreover, has been favored since 1931 by the use of the sedimentation rate of erythrocytes as an indication of the existence of active infection. That slow but definite progress has been made toward the goal of prolonged care for the child when it is first taken ill with rheumatic infection, without regard to the existence of clinically recognizable heart disease, is indicated by the fact that such children have been kept on the wards for increasing periods of time (Table IX).

TABLE IX

DURATION OF HOSPITAL STAY: 189 PATIENTS WITH POLYARTHRITIS OR CARDITIS
ADMITTED DURING FIRST YEAR OF RHEUMATIC INFECTION

YEARS OF ONSET	10 OR MORE WEEKS		6 OR MORE WEEKS		4 OR LESS WEEKS		TOTAL NUMBER OF PATIENTS
	NO.	%	NO.	%	NO.	%	
1922-26	9	19.6	19	41.3	26	56.5	46
1927-31	16	24.6	33	50.7	29	44.6	65
1932-36	26	32.5	53	67.9	21	26.9	78

The value of prolonged bed rest in lessening the incidence of noticeable rheumatic heart disease has been demonstrated in London,⁵ where, as a result of cooperative effort between school and health authorities, beds were provided in sufficient number to permit hospitalization of all patients with rheumatic fever, chorea, or active rheumatic heart disease, who were under 16 years of age, for a minimum period of six months, followed by adequate convalescent care and continued supervision in special centers. After this program for supervision of rheumatic children was begun, the incidence of heart disease among school children in London dropped from 2 per cent in 1926 to 0.8 per cent in 1936—a decline of 60 per cent.

That the use of a convalescent home for cardiac children is no panacea, if not preceded by an adequate period of hospitalization, has been demonstrated by experience with eighty-seven rheumatic patients who were transferred from the Children's Hospital to the Philadelphia

Heart Hospital (Table X). All children at the Heart Hospital are kept in bed for varying periods after admission, and are only gradually permitted to engage in full activity. Lavatory privileges, however, are granted from the time of admission. During the early years, many patients from the Children's Hospital were transferred to the Heart Hospital while they still had evidence of acute infection. A large proportion of these were returned with recrudescences, or with a more severe degree of functional incapacity. The death rate among such children was high. Apparently, a convalescent home is no substitute for the hospital in the case of a child with active infection, although it may serve a valuable purpose in ensuring continued supervision, adequate rest, proper diet, and schooling for the underprivileged child who has recovered from an acute attack of rheumatism. When so used, it is possible that such children may be brought into a state of good health that will insure stabilization of the infection. The subject is almost academic, however, because, save perhaps in London (prior to the present war), there have been no provisions for an adequate number of beds for long-continued hospital and convalescent care for the rheumatic child.

TABLE X

COURSE OF 87 RHEUMATIC PATIENTS TRANSFERRED TO HEART HOSPITAL

YEARS OF ONSET	NUMBER OF PATIENTS	ACTIVE INFECTION %	CLASS 11B %†	RETURNED TO HOSPITAL	WITHIN 3 YEARS	
					HRT. DIS. %	DEATHS %
1922-26	41	53.7	46.3	39.0	87.8	19.5
1927-31	27	40.7	33.3	3.7	80.1	3.7
1932-36	19	31.6*	15.8	5.2	82.4	5.2

*Active infection in children transferred during 1932-36 was usually low-grade or subclinical, in contrast to the relatively acute degree of infection which was present in many of the children who were transferred to the Heart Home during 1922-26.

†Class 11B (old terminology) indicates greatly limited physical activity due to cardiac disease.

It is the present policy of the Children's Hospital to refer to the Heart Hospital only children with minimum or moderate heart damage, who are convalescent from a first, or, at most, a second, attack of the disease, preferably with inactive infection.

Within recent years, moreover, tonsillectomy has no longer been a routine procedure in the treatment of the rheumatic child. Tonsils are now removed only when there is evidence of tonsillar disease. The operation is performed during an inactive phase of the rheumatic infection.

SUMMARY

The course of 583 children who suffered from rheumatic infection which originated during the years 1922 to 1936 has been described. Ninety-four and eight-tenths per cent of these children have been followed for a minimum period of three years and an average period of 9.6 years since the primary manifestation. At the end of this time, 64.2

per cent presented signs of valvular heart disease and 21.7 per cent had died of rheumatic infection. An additional 3.5 per cent had died of bacterial endocarditis or other infection associated with active rheumatism.

The course of the disease was modified by the type of onset; acute carditis presented the most ominous prognosis and chorea the most favorable. Children with a diagnosis of potential heart disease at the onset frequently tended to retain their freedom from signs of heart disease, in spite of recurrences.

A trend toward a decrease in the severity of rheumatic infection has been noted during the period of observation; this has been manifest especially among patients whose primary symptoms were arthritic.

This improvement in the course of the disease cannot be ascribed to racial variation, relative changes in type of onset, progressive decline in recurrences, or a modification of the policy of the hospital in regard to admissions. Although it is part of a downward trend in mortality from heart disease among young people throughout the United States registration areas, the decrease in mortality at the Children's Hospital has been greater than that in Pennsylvania as a whole.

Within recent years an attempt has been made at the Children's Hospital to concentrate attention on the child with the first manifestation of rheumatism, however mild. Such children have been kept at rest in bed and their activity restricted for longer periods of time. Whether such intensive supervision of the child with early signs of the disease has accelerated the natural trend to improvement is a subject for speculation.

A recently adopted, conservative attitude toward tonsillectomy seems at least to have had no unfavorable influence.

The experience at the Children's Hospital with patients who were transferred to a convalescent home would seem to indicate that, although such convalescent care may serve a valuable purpose in ensuring stabilization of the infection in the child who has recovered from an acute attack, it is no substitute for absolute bed rest for the child with any degree of active infection.

In spite of the seeming decline in severity, rheumatic infection still remains the most serious disease which attacks children past the age of infancy.^{5, 6} In the most favorable period of the present study (1932-36), almost 7 per cent of the rheumatic children had died by the end of the first year, and 10 per cent by the end of the third year, at which time 50 per cent of the group had presented obvious signs of rheumatic heart disease.

I am indebted to the physicians and social workers from whom information was obtained; their number is too great to permit individual mention. I owe a special debt to the workers in the Social Service Department of the Children's Hospital, without whose aid many of these children could not have been traced.

REFERENCES

1. Ash, R.: Prognosis of Rheumatic Infection in Childhood. A Statistical Study, *Am. J. Dis. Child.* 52: 280, 1936.
2. Criteria for the Classification and Diagnosis of Heart Disease, New York, 1932.
3. Wilson, M. G.: Clinical Radioscopic Studies of the Heart in Children, *Am. J. Dis. Child.* 47: 750, 1934.
4. Hedley, O. F.: Trends, Geographical and Racial Distribution of Mortality From Heart Disease Among Persons 5-24 Years of Age in the United States During Recent Years (1922-1936), *Pub. Health Rep.* 54: 2271 (Dec. 29), 1939.
5. London County Council Annual Report (Part 2, Public Health), 1937, quoted by Swift, H. F.: Public Health Aspects of Rheumatic Heart Disease, *J. A. M. A.* 115: 1509, 1940.
6. Hedley, O. F.: Mortality From Rheumatic Heart Disease in Philadelphia During 1936, *Pub. Health Rep.* 52: 1907 (Dec. 31), 1937.

FURTHER OBSERVATIONS ON THE MECHANISM OF THE PRODUCTION OF A SHORT P-R INTERVAL IN ASSOCIATION WITH PROLONGATION OF THE QRS COMPLEX

CHARLES C. WOLFERTH, M.D., AND FRANCIS C. WOOD, M.D.
PHILADELPHIA, PA.

ALTHOUGH Wolff, Parkinson, and White¹ were not the first to report cases of short P-R intervals in association with prolonged, aberrant QRS complexes, these workers deserve the credit for directing attention to this anomaly, for making the first systematic study of it, and for pointing out that it may be found in presumably healthy persons. However, their assumption that bundle branch block is present precipitated a controversy which has continued since that time. Holzman and Scherf² and we,³ independently, suggested that the anomaly might be explained by assuming that there is an accessory pathway of conduction between auricles and ventricles. We were unwilling to accept the hypothesis of bundle branch block because patients who have both normal and abnormal complexes are likely to show the same interval between the beginning of the P wave and the end of the QRS complex in both.

We shall not review the literature on the mechanism of short P-R interval and prolonged QRS complex, for this has been done many times, and again recently by Hunter, Papp, and Parkinson.⁴ It is of interest that Parkinson has changed his view as to the mechanism of this condition. He no longer believes that it is a form of bundle branch block. He stresses the fact that in certain cases the P waves preceding the aberrant complexes may differ in shape from those preceding the normal complexes and states that any hypothesis should explain (1) the difference in the shape of P before normal and short P-R, bundle branch block* complexes, (2) the peculiar shape of the ventricular complex, as compared with that of ordinary branch block, and (3) the gradual change of P and QRS from short P-R, bundle branch block to normal (after atropine), and the appearance of intermediate ventricular complexes. Hunter, Papp, and Parkinson state that previous explanations did not adequately account for these facts, and they reject, among other hypotheses, that of an accessory pathway of A-V conduction. They suggest as an alternative explanation that, when the anomaly is present, the beat arises near, but not in, the normal pacemaker (for the P wave is altered)

From the Robinette Foundation, Medical Division, Hospital of the University of Pennsylvania.

Received for publication Jan. 17, 1941.

*Short P-R interval with bundle branch block complexes.

and that the normal ventricular complex is interfered with by a ventricular extrasystole which arises prematurely, low in one bundle branch. They state, "In our view the upper impulse would spread only to the ventricle other than that producing the extrasystole."

When we analyze this hypothesis, we must first admit that it could account for the aberrant complexes. Furthermore, it does away with the untenable idea of bundle branch block. The tendency of these patients to develop forms of paroxysmal arrhythmia is ascribed by these authors to hyperexcitability of the conducting tissue. They do point out, however, that the absence of ventricular extrasystoles in their cases is not in accord with the assumption of hyperexcitability.

There is one objection to the hypothesis of Hunter, Papp, and Parkinson which appears to us insurmountable. It is necessary to postulate that an ectopic ventricular beat is capable of bearing a constant time relation to an auricular beat which must be arising independently of it. Such a time relation must be maintained, not just momentarily, as might occur by chance, but over long periods of time. It appears to us that the mathematical probability of such an occurrence, not alone in one case, but in all cases of this anomaly, is not great.

Recently we have encountered a patient with this syndrome whose electrocardiogram seems to furnish further evidence on this question. In this patient's tracing (Fig. 1) the anomaly of short P-R interval and prolonged, aberrant QRS complex is exhibited. Frequent auricular extrasystoles are present, and the shape of the premature P waves differs from that of the regular P waves. The P-R intervals of the premature beats appear to be even shorter than those of the ordinary beats, but there is no essential change in the contour of the ventricular complexes. (There is a slight increase in their duration, which will be discussed below.)

This case, and a similar one reported by Scherf and Schönbrunner,⁵ seem to us to add considerably to the difficulty of accounting for the syndrome on the hypothesis advanced by Hunter, Papp, and Parkinson.⁴ In order to explain the aberrant ventricular complex following each auricular premature beat, one would have to assume that, whenever an auricular extrasystole occurs, a ventricular extrasystole (which must arise independently) selects the exact relative moment for its origin, which will produce a ventricular complex like all the others. Such a possibility seems to us so incredible that we believe this hypothesis, like that of bundle branch block, must be abandoned.

The question might be raised whether the behavior observed in these premature beats does not also constitute an objection to the hypothesis of an accessory pathway of conduction. In our opinion it not only does not constitute an objection, but offers further evidence in favor of it.

When a beat arises in the sinus node, the excitation process presumably travels in the manner described by Lewis to all parts of the auricles, and, in due course of time, reaches the auriculoventricular node and the accessory conduction tract, if there be such a structure. If, however, the impulse arises elsewhere in the auricles, the relative time of arrival at these two structures might remain undisturbed but is much more likely to be somewhat altered. The latter apparently occurred in our case, for the QRS complex is very slightly widened, although the P-R interval is much shorter. This suggests that the extrasystoles arose in a position relatively nearer to the accessory conduction tract than to the A-V node.

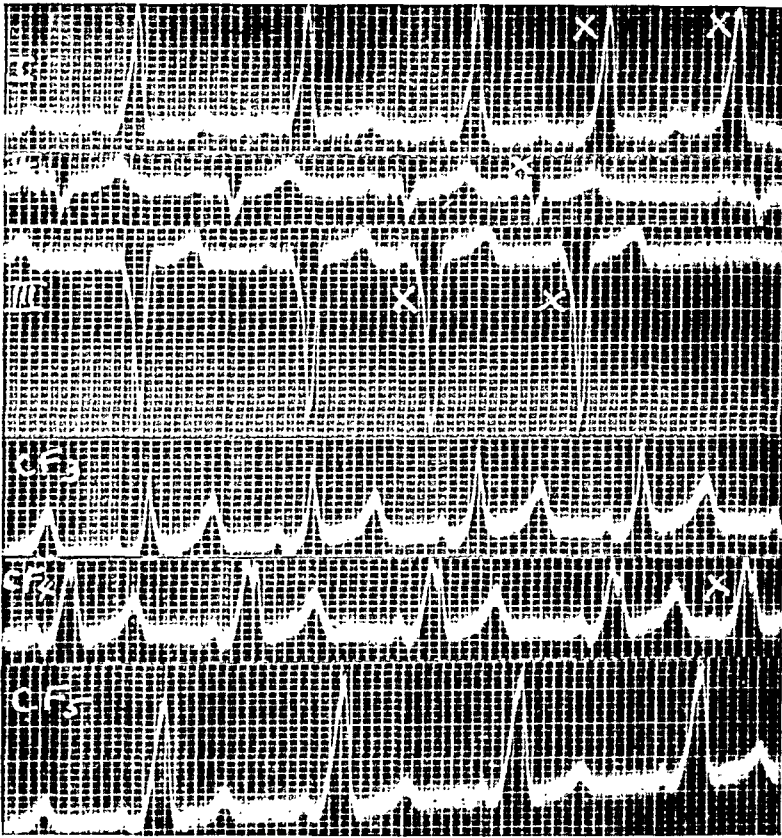


Fig. 1.—Electrocardiogram of R. M. H., a 42-year-old man who had rheumatic heart disease, with mitral insufficiency and stenosis. He had been seen on four different occasions. On Nov. 20, 1939, he had auricular fibrillation; on July 16, 1940, auricular flutter; and, on Sept. 28, 1940, normal sinus rhythm. No abnormality of the QRS complex was seen on any of these occasions. On his fourth visit Nov. 27, 1940 his tracing (reproduced here) showed the syndrome of short P-R interval and widened, slurred QRS complexes. At points marked X, auricular extrasystoles occurred. It will be noted that the contour of the QRS complex after each auricular extrasystole is substantially like that after the regular auricular beats, despite the fact that the P-R interval is shortened.

Holzman and Scherf² have suggested one other possible explanation for this syndrome of short P-R interval and aberrant QRS, i.e., that normal auricular contraction might stimulate mechanically an excitable focus in one ventricle. This seems highly unlikely for the following reasons: (1) This hypothetical phenomenon has never been observed in patients with heart block. (2) Although one (C. C. W.) of us, with Mc-Millan, some years ago attempted to bring it about experimentally, suc-

cess was never achieved; nor do we know of its ever having been produced or observed in animals. (3) The P-R interval in Fig. 1 is shorter after the auricular extrasystoles than after the regular auricular beats. If mechanical stimulation of ventricle by auricle were taking place, the P-R interval should be essentially the same in both.

It might be worth while, in the light of recent observations, to review the present status of the hypothesis of an accessory pathway of A-V conduction. It still seems to us to be the most satisfactory explanation for this syndrome, and we have found no reason to change, in any material way, the views we expressed in our former paper.³ In a recent paper, Glomset and Glomset⁶ demonstrated the existence of accessory neuromuscular connections between auricles and ventricles. Thus the anatomic background for the hypothesis has been re-emphasized. One of the main reasons why Hunter, Papp, and Parkinson reject the "accessory pathway" hypothesis is because they found that, in certain cases, the P wave changed its contour when the aberrant ventricular complexes gave place to normal ones. Although this occurrence would not constitute a vital objection, it would be an unexpected feature if the hypothesis of an accessory conduction pathway were true. Consequently, we have consulted the papers cited by Hunter, Papp, and Parkinson in order to study the alterations in the P waves which they described. We were unable to find one of these papers, namely, that by Fernbach.⁷ In the paper by Pines⁸ there are no electrocardiograms. In the tracings published by Scherf and Schönbrunner,⁵ the P waves do not change in the slightest way that we can see. In the tracings published by Zarday,⁹ we see no change in the P waves. In the tracings published by Moia and Inchauspe,¹⁰ there are technical defects in the curves which make analysis difficult, but one finds as much variation between the various P waves preceding the aberrant ventricular complexes as one finds when one compares them with the P waves preceding the normal complexes. In the tracings reproduced in the paper by Tung,¹¹ a rather interesting phenomenon is observed. Twenty minutes after the administration of atropine the P waves became smaller than they were before, and the QRS complexes returned to normal. Yet, thirty minutes after the administration of atropine, the QRS complexes were still normal, whereas the P waves had returned to their former contour. Furthermore, they retained that contour during the subsequent transition of the ventricular complexes from normal back to the aberrant configuration. This suggests that the P-wave change observed might be associated with the effect of atropine, rather than with the change of mechanism. Finally, let us study the tracings of Hunter, Papp, and Parkinson.⁴ They state that P-wave changes occurred in Cases 1, 3, 5, 18, and 20. They published the tracings of Cases 1, 3, and 20. The first two show minor changes in P, not striking variations. Case 20 shows the only definite change; an inverted P in Lead I becomes upright. *But this is not an example of the*

syndrome we are discussing; it shows no abnormality in the ventricular complex! Thus, after attempting a careful review of the evidence, we are impressed, not with the change which occurs in the P wave when the contour of the ventricular complex changes, but rather with the fact that the P wave shows such a remarkable constancy of contour throughout. It does not change except in minor details, which might well be explained as a result of exercise, atropine, deep breathing, or any of the other maneuvers which have been used in these cases to bring about a change in the ventricular complexes. We can say with conviction that the shape of the P waves is as constant in this group of patients, regardless of the shape of the ventricular complex, as it is in a series of tracings from patients with normal sinus rhythm.

Finally, Hunter, Papp, and Parkinson object to the hypothesis of an accessory pathway of A-V conduction on the ground that they observed ventricular complexes which were intermediate in shape between the two extremes. They state that, according to this explanation, there should be two distinct types of curves and no intermediate ones. However, according to our view, the existence of intermediate types of complexes would fit in perfectly well with the "Bundle of Kent" hypothesis. There are at least three mechanisms by which intermediate complexes might arise: (1) By a change in the conductivity of the accessory tract, (2) by a change in the conductivity of the bundle of His (in which case the time from the beginning of P to the end of QRS might change), and (3) by a shift of the pacemaker in the auricles from its usual location to a position relatively nearer to the A-V node than to the accessory tract, or vice versa. The first explanation may be the usual one. If the accessory pathway becomes less conductive under certain circumstances, one might expect the diminution of conductivity to occur gradually, with a corresponding, gradually increasing delay in the transmission of the excitatory process to the ventricular muscle. As this takes place, the area in the ventricle which is excited through the accessory pathway should become gradually smaller, and that which is excited through the bundle of His should become gradually larger. This would seem to furnish adequate reason for a gradual change in the shape of the ventricular complex as it goes from normal to abnormal.

Our conclusions are, therefore, that the hypothesis of an accessory pathway of A-V conduction is the most satisfactory one yet proposed. We have encountered no evidence to lead us to discard it. Moreover, we have not as yet heard of an alternative hypothesis which explains the phenomena observed in these cases.

There are certain other points which might be worth mentioning at this time. With regard to the question whether the part of the ventricular muscle which is activated through the accessory pathway is in the right or in the left ventricle, we³ presented evidence suggesting that it was in the right. We now question whether this is completely justified.

Study of the electrocardiograms of right bundle branch block shows that T waves in the limb leads frequently fail to show abnormalities. This suggests that the right ventricle plays a minor part in the formation of limb lead T waves. Furthermore, in chest leads made from the C_5 position, that part of the QRS complex which is attributable to right ventricular activity is usually very small. However, in some cases of the short P-R interval and aberrant QRS syndrome, T-wave changes appear in limb leads. Moreover, in some the initial portion of the QRS complex in lead CF_5 is large. It seems likely to us, therefore, that, when

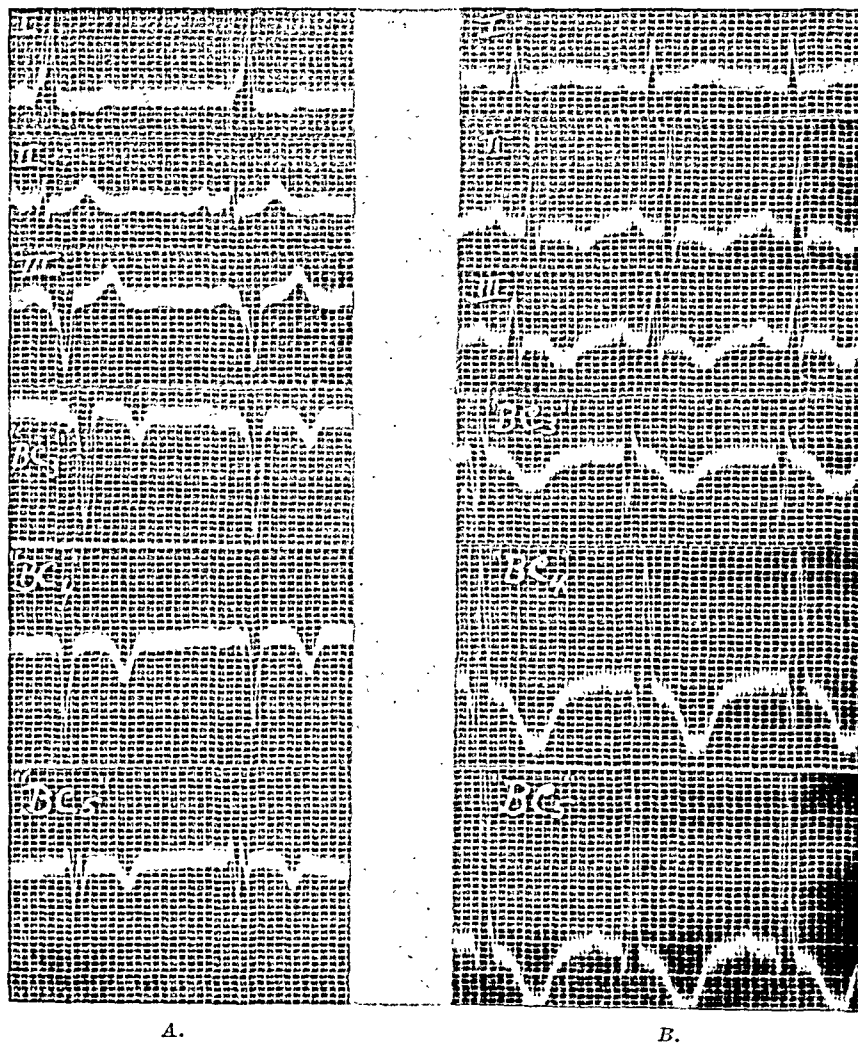


Fig. 2.—Electrocardiograms of A. B., a 26-year-old man, taken on Sept. 15, 1936 and Sept. 16, 1936. (This patient was described as "Case 3" in our former paper.) A, Tracing taken before quinidine administration on Sept. 15, 1936, showing a short P-R interval and widened, slurred QRS complexes.

He was given 40 grains of quinidine sulphate between 8 A.M. and 2 P.M. on Sept. 16, 1936. B, Tracing taken at 3 P.M., showing a normal P-R interval and a disappearance of the abnormality of QRS. The T-wave inversion may be a quinidine effect. Previously we had not been able to bring about a disappearance of the abnormal QRS complexes by amyl nitrite administration or by exercise. The chest leads in these tracings were taken with a polarity opposite to that now recommended by the Committee of the American Heart Association for the standardization of precordial leads. BC_3 , BC_4 , and BC_5 were taken with the right arm electrode on the precordium at C_3 , C_4 , and C_5 positions, respectively; the other electrode was near the angle of the left scapula.

large initial QRS deflections occur at the C_5 position, or when inversion of T_1 appears, the accessory conduction tract may be leading directly to the left ventricle, or that, at least, the excitation wave may be reaching a part of the left ventricle before that chamber is completely activated through the bundle of His.

We wish to call attention to an observation reported by Roberts and Abramson,¹² in 1936, which has not been confirmed heretofore. In a patient with this syndrome they were able to change the contour of the electrocardiogram from abnormal to normal by the administration of quinidine. We tried this same procedure on one of our patients and observed similar results (Fig. 2). The patient was described as Case 3 in our former paper.³ On Sept. 15, 1936, he took quinidine sulphate as follows: 5 gr. at 8 A.M., 10 A.M., 12 M. and 2 P.M. (20 gr. in all) without effect. On Sept. 16, 1936, he took double the dose (10 gr. at 8 A.M., 10 A.M., 12 M., and 2 P.M.) and at 3 P.M. showed normal QRS complexes; we had been unable to bring about this change by exercise or by amyl nitrite administration. Roberts and Abramson carried out this procedure because quinidine, which is known to diminish conduction in the heart, might affect the accessory pathway more readily than it would affect the bundle of His. It should be stated, however, that quinidine also reduces the irritability of the myocardium. Consequently, this therapeutic result cannot be used as an argument in favor of the hypothesis of an accessory pathway of conduction, as opposed to that of Hunter, Papp, and Parkinson.

Finally, Scherf and Schönbrunner⁵ report that, in one of their cases, large doses of digitalis caused the abnormal QRS complexes to disappear for a period of three weeks. This result might indicate that the accessory pathway is more susceptible to digitalis than the bundle of His.

SUMMARY

The syndrome of short P-R interval and prolonged QRS complex is re-examined in the light of recent observations. The hypothesis of an accessory pathway of A-V conduction is the only one thus far advanced which explains the phenomena observed in these cases.

A case is reported in which QRS maintained its abnormal contour after auricular extrasystoles. This observation renders the hypothesis of Hunter, Papp, and Parkinson even more incredible than it had seemed to us before.

Contrary to the reports of Hunter, Papp, and Parkinson, we find that the contour of the P wave is remarkably constant in these cases when the ventricular complexes change their shape.

Certain facts are presented which lead us to believe that the part of the ventricular myocardium which is activated through the hypothetical accessory pathway may not be confined strictly to the right ventricle in all cases.

The fact that quinidine will change the complexes of the electrocardiogram from abnormal to normal, as reported by Roberts and Abramson, was confirmed in one of our cases.

REFERENCES

1. Wolff, L., Parkinson, J., and White, P. D.: Bundle-Branch Block, With Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, *AM. HEART J.* 5: 685, 1930.
2. Holzman, M., and Scherf, D.: Über Elektrokardiogramme mit verkürzter Vorhof-Kammer-Distanz und positiven P-Zacken, *Ztschr. f. klin. Med.* 121: 404, 1932.
3. Wolferth, C. C., and Wood, F. C.: The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients With Presumably Undamaged Hearts: Hypothesis of an Accessory Pathway of Auriculo-Ventricular Conduction (Bundle of Kent), *AM. HEART J.* 8: 297, 1933.
4. Hunter, A., Papp, C., and Parkinson, J.: The Syndrome of Short P-R Interval, Apparent Bundle Branch Block, and Associated Paroxysmal Tachycardia, *Brit. Heart J.* 2: 107, 1940.
5. Scherf, D., and Schönbrunner: Beiträge zum Problem der verkürzten Vorhofkammerleitung, *Ztschr. f. klin. Med.* 128: 750, 1935.
6. Glomset, D. G., and Glomset, A. T. A.: A Morphologic Study of the Cardiac Conduction System in Ungulates, Dog, and Man, *AM. HEART J.* 20: 389, 1940.
7. Fernbach, J.: *Orvosi hetil.* 81: 377, 1937 (Quoted from⁴).
8. Pines, W.: Ein Fall von funktionellem Schenkelblock während der Schwangerschaft, *Wien. Arch. f. inn. Med.* 32: 129, 1938.
9. Zarday, I.: Ungewöhnliche Vorhofkammerleitung, *Ztschr. f. Kreislaufforsch.* 29: 208, 1937.
10. Moia, B., and Inchauspe, L. H.: Sobre un caso de P-R corto con QRS ancho y mellado presentando asynchronismo ventricular, *Rev. argent. de cardiol.* 5: 114, 1938.
11. Tung, C. L.: Functional Bundle Branch Block, *AM. HEART J.* 11: 89, 1936.
12. Roberts, G. H., and Abramson, D. I.: Ventricular Complexes of the Bundle-Branch Block Type Associated With Short P-R Intervals, *Ann. Int. Med.* 9: 983, 1936.

ARTERIOSCLEROTIC ANEURYSMS AND SENILE ECTASIA OF THE THORACIC AORTA

MARSHALL DE G. RUFFIN, M.D., BENJAMIN CASTLEMAN, M.D., AND
PAUL D. WHITE, M.D.
BOSTON, MASS.

DEATH from internal hemorrhage, caused by rupture of the thoracic aorta in two old women with nonsyphilitic, thoracic, aortic aneurysms during the past year, has been of such unusual interest to us that we have surveyed the literature and analyzed the post-mortem records of the Massachusetts General Hospital to assemble further information about such aneurysms. The first case was one of arteriosclerotic aneurysm; the second, one of dissecting aneurysm in an aorta which was the seat of senile ectasia. We shall first present the two case histories.

CASE 1.*—(A.P.G.) A 78-year-old widow received medical attention because she was extremely nervous and mentally disturbed following an attack of vomiting. On examination she had a temperature of 101.5° F., a pulse rate of 92, a red throat, and occasional fine râles in both lungs. Her heart was within normal limits as to size, a systolic murmur was audible over the whole precordium, and there was an occasional extrasystole. The left patellar reflex was slightly greater than the right; the other tendon reflexes were normal. A blood smear showed an elevated polymorphonuclear count, but was otherwise negative. A diagnosis of mild upper respiratory infection was made. The patient was seen again a short time later by her physician because of increasing nervousness resulting from business strain; physical examination at that time showed no definite abnormalities. The blood pressure was 145/95.

A year and a half later she was examined because of fatigability, occasional shortness of breath, and slight orthopnea; she used two pillows at night. The heart borders, by percussion, were then found to be 9 cm. to the left and 3 cm. to the right of the median line. There was accentuation of the second sound, which was marked at the aortic valve area and moderate over the pulmonic valve. A short systolic murmur was heard over the whole precordium. The pulse rate was 96; the blood pressure was 140/80. The bases of the lungs were clear; the edge of the liver was not palpable; there was no edema of the ankles. After still another fifteen months she was observed after an attack of "grippe" that was accompanied by persistent pain in the region of the lower ribs on the left which

From the Department of Pathology and Bacteriology and the Medical Service of the Massachusetts General Hospital, Boston, Mass.

Presented before the New England Heart Association at the Massachusetts General Hospital, Boston, Dec. 16, 1940.

Received for publication Jan. 29, 1941.

*We wish to thank Dr. H. D. Stebbins, of Marblehead, Mass., for permission to use this case, which one of us (P. D. W.) saw in consultation with him. This case was discussed in detail in the Case Records of the Massachusetts General Hospital, Case 25521, *New England J. Med.* 25: 1030, 1939.

lasted about six days. Physical examination revealed an increase in the antero-posterior diameter of the chest, with hyperresonance except at the left base below the midscapular region, where there was slight dullness, with vesicular breath sounds throughout, without râles, but with a slight decrease in the intensity of the breath sounds below the left scapula. The border of cardiac dullness was 8 cm. to the left of the midline in the fifth intercostal space and 3.5 cm. to the right in the fourth. The sounds were distant but clear. There were no murmurs. The blood pressure was 130/80 in both arms, and 150/90 in both legs. There was no tracheal tug. The pupils were equal and reacted to light and in accommodation. The peripheral vessels showed a rather marked degree of arteriosclerosis. A roentgenogram of the chest (Fig. 1), made with a portable machine, showed a large round mass, apparently continuous with the heart shadow, occupying the entire middle third of the left lung field. An electrocardiogram showed a sinus tachycardia of 135 beats per minute, with left axis deviation (-22°), a P-R interval of 0.13 sec., and notched P_2 and P_4 ; QRS_1 and QRS_2 were of fairly low voltage (6 mm. and 5 mm., respectively); the S-T segments in Leads I and II sagged slightly; T_1 and T_2 were upright; T_3 was shallow and inverted; R_4 was present; and T_4 was upright. A blood Wassermann reaction was negative.

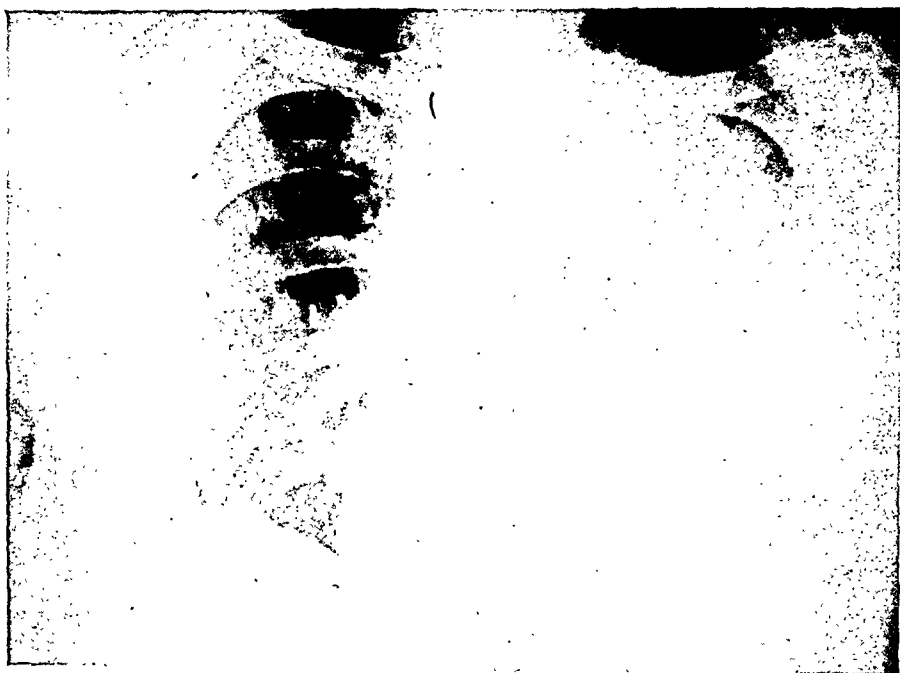


Fig. 1.—Roentgenogram of thorax of A. P. G., Case 1 (aged 82), showing large aneurysm of the descending thoracic aorta.

Three months later, at the age of 82 years (four years after her first complaints), she spent a busy day shopping, apparently feeling quite well. She went to bed at 9:00 P.M. after a good New England supper of baked beans and brown bread, and slept quietly until midnight, when she suddenly awoke complaining of severe pain in the mid-upper back and chest. She became extremely orthopneic and dyspneic. On the arrival of her physician, a few minutes later, she was found sitting up in bed breathing forty to fifty times per minute. Her pulse rate was 140, and the pulse was weak. She was wild-eyed and had an ashen cyanosis, with cold sweat. The peripheral veins were not distended. The heart sounds were distant but clear. There were no murmurs. The lungs were clear throughout; there were no râles even at the extreme bases. The abdomen was negative. The patient

was given $\frac{1}{4}$ grain of morphine sulfate and 1/150 grain of atropine sulfate subcutaneously. Although the rapid respiration persisted, she soon became unconscious. At about 1 A.M. the radial pulse became imperceptible and the blood pressure could not be measured. Oxygen was given for an hour. An electrocardiogram showed a ventricular and auricular rate of about 130, with slight left axis deviation, upright T_1 and T_2 , and an inverted T_3 ; the P-R interval was 0.15 sec., with slightly elevated S-T segments in Leads I, II, and III, and low QRS voltage. The patient was given coramine and caffeine sodium benzoate, but expired about two and a half hours after the onset of the attack. The clinical diagnosis was ruptured aneurysm of the thoracic aorta.

The autopsy revealed the body of a well-developed and nourished, moderately obese, 82-year-old, white woman who had multiple arteriosclerotic saccular aneurysms of the aorta, with rupture of one in the descending thoracic portion into the right pleural cavity. There resulted a massive hemothorax containing approximately 2 liters of fresh, deep-red blood, some of which had clotted post mortem. When this blood was removed and the right lung pulled forward, the mediastinal parietal pleura along the anterior portion of the thoracic vertebrae was seen to be colored purplish red by blood which was beneath it. In this region, at the level of the fourth dorsal vertebra, there was a triangular tear, measuring 1 by 0.5 cm., which was apparently the source of the pleural hemorrhage. The left pleural cavity contained approximately 200 c.c. of clear, straw-colored fluid. The lower two-thirds of this cavity were replaced by a large lobular mass, measuring 12 by 12 by 8 cm., which compressed the lower lobe of the left lung and produced definite atelectasis. The remainder of the lungs and the heart were not remarkable. The ascending portion of the thoracic aorta was fairly smooth and showed no aneurysm. The arch revealed moderate arteriosclerosis, with some ulceration. Most of the descending thoracic portion of the aorta was composed of a huge aneurysmal sac which extended out from the left lateral wall. This aneurysm measured 12 cm. in length by 12 cm. in width, and had a round opening into the aorta of a diameter of 8 cm. It was completely filled with grayish-red, solid thrombus. On the right anterior lateral wall of the aorta, at a point approximately level with that of the aneurysm, the intima was completely denuded and eroded over an area measuring 5 by 3 cm. This area was covered by a yellow-gray, friable mural thrombus. There was another similar area, about 1 by 5 cm. in extent, just medial to the larger erosion. Blood clot from the aneurysm extended beneath the former erosion around the posterior aspects of the aorta into the right side, through which it ruptured into the right side of the thorax via the mediastinal parietal pleural tear previously noted. Over the lower lumbar vertebrae there was a large firm mass, 12 cm. in length by 5 cm. in width, which, when removed, was found to be another atherosclerotic aneurysm with an aortic opening about 6 cm. in diameter. It involved the whole anterior portion of the aorta and was filled with firm, red-gray thrombus. There was still another aneurysm, 5 by 5 cm. in diameter, involving the left common iliac artery. The aorta between the aneurysms showed marked arteriosclerosis throughout, with ulceration and small mural thrombi. The other gross anatomic abnormalities were of little import. Microscopically, sections through the aneurysms showed marked fibrous intimal proliferation, slight lymphocytic infiltration of the media, and an old organized thrombus attached to the intima. There was no evidence of syphilis.

CASE 2.—(M. Van d.P.) A 71-year-old housewife entered the hospital in January, 1934, because of shortness of breath of a month's duration. For ten years the patient had experienced slight shortness of breath and occasional staggering while walking. Her physician had found hypertension and had treated her with "powders" and tablets. During the month preceding admission, however, she

noted increased dyspnea and palpitation and a feeling of constriction in the precordial region on slight exertion. She also noticed pyuria, burning urination, and a foul odor to the urine.

The examination showed generalized arteriosclerosis, but no congestive failure. The heart was moderately enlarged, and there was a questionable systolic thrill to the right of the upper end of the sternum. The apical impulse was vigorous. Maximal to the right of the upper and middle portions of the sternum was a loud, harsh, systolic murmur. The aortic second sound was present, and was followed by a slight to moderate diastolic murmur. The heart rate was 70 per minute, with frequent premature beats. The blood pressure was 165/96, and alternation was present. An electrocardiogram showed auricular premature beats, a rate of 60 to 65, a diphasic T₁, and moderate left axis deviation.

She remained in the hospital for two weeks, and was discharged improved, on digitalis, with a diagnosis of hypertensive and calcareous valvular heart disease, with aortic stenosis and regurgitation.

Second admission, September, 1936. This illness was apparently due to cholecystitis and pneumonia, which precipitated an ectopic auricular tachycardia at a rate of 340, with 2 to 1 block and mild failure. She was seriously ill for two weeks. The block was increased to 4 to 1 with digitalis. Later, auricular fibrillation appeared, and, still later, normal rhythm returned spontaneously. The patient was greatly improved. The lung signs disappeared, and, although mild attacks of abdominal discomfort continued, it was felt that surgical treatment was not indicated.

In November, 1936, the patient returned for examination feeling quite well except for a little indigestion (occasional gaseous distention and mid-abdominal pain). She looked well. Her pulse was regular at a rate of 72. Her blood pressure was 160/80. The heart was large, and there were moderately loud aortic systolic and diastolic murmurs, with slight thrills palpable in both systole and diastole. The aortic second sound was accentuated. The electrocardiogram showed normal rhythm, a rate of 65, moderate left axis deviation, and sagging S-T segments in Lead I (a digitalis effect). Fluoroscopic examination revealed a big, round, active heart, with a very dense, dilated, actively pulsating ascending aorta. The lung hila were normal in appearance. By orthodiagram, the transverse diameter of the heart measured 14.6 cm. and the internal diameter of the thorax 21.5 cm.; the width of the great vessels in the anteroposterior view was 8.3 cm.

On June 29, 1937, at the age of 75, she had a paroxysm of auricular fibrillation during a routine examination, and her heart and aorta were somewhat larger than the year before; a note was made that, fluoroscopically, the ascending aortic shadow resembled that of an aneurysm.

In January, 1938, she complained only of occasional palpitation, not of pain or dyspnea. Her heart was larger, measuring 16.1 cm. in its transverse diameter by orthodiagraphy. The electrocardiogram now showed inversion of the T waves in Leads I and IV, in addition to considerable left axis deviation.

In June, 1938, she at last showed frank heart failure, which had begun with orthopnea at night a week before. She had been seriously ill with grippe and pneumonia in April. Examination revealed moderate edema of both feet, an increased jugular pulsation, a blood pressure of 145/90, a larger heart (16.6 cm. transverse diameter by orthodiagraphy), and a pulse rate of 84, with occasional extrasystoles.

With rest and digitalis the failure subsided, and, in December, 1938, she was well except for dyspnea on effort. Examination revealed no congestion except of the hila of the lungs, as shown by fluoroscopic examination. The murmurs over the aortic valve area were now clearly continuous, with a systolic accentuation and thrill. Aneurysmal dilatation of the ascending aorta was evident fluoroscopically,

and, because of the change in the character of the murmur and the development of heart failure, a question was raised as to dissection or rupture.

The last routine examination took place in June, 1939. She had been fairly well through the winter except for dyspnea and weakness. There had been no cough or chest pain. The continuous murmur and thrill over the aortic valve area were more evident than before. Fluoroscopic examination showed kinking and bulging of the descending aorta as well as aneurysmal dilatation of the ascending aorta, and a diagnosis of probable arteriosclerotic aneurysmal disease of the aorta with questionable rupture into the right side of the heart or pulmonary artery was made. A roentgenogram (Fig. 2) showed marked enlargement of the heart on both sides, but chiefly in the region of the left ventricle. The aorta was markedly tortuous, dilated, and calcified. A lateral view (Fig. 3) showed the marked dilatation of the ascending aorta and the extreme calcification of the arch and descending portions. She went to California that summer and, after returning, was confined to her home because of dyspnea. In November, 1939, she quietly passed away without any noticeable signs to suggest rupture of an aneurysm.



Fig. 2.—Roentgenogram of thorax of M. Van d.P., Case 2 (aged 76), showing senile ectasia of the ascending aorta, marked calcification of the aortic arch, and a very large heart.

The post-mortem examination revealed a well-developed and moderately well-nourished, previously embalmed, 76-year-old woman who weighed approximately 100 pounds. The lungs showed apical scars and slight but definite emphysematous changes. There were no areas of consolidation. A few large blood clots, measuring altogether roughly 7 by 3 by 2 cm., were found high in the pericardial cavity, especially surrounding the aorta and pulmonary artery. The heart weighed 500 grams. The right ventricular wall measured 7 mm. in thickness, the left, 20 mm. There was marked hypertrophy of the left side of the heart; the right ventricle formed only a small portion of the anterior surface. *All of the valves were normal.* The coronary arteries showed moderate arteriosclerotic changes, with calcification in many places, but no evidence of occlusion. The whole ascending aorta was

markedly dilated, forming a diffuse aneurysm which measured approximately 12 cm. in circumference. The intima was smooth throughout, with very little atheroma and no scarring. There were numerous trocar incisions (embalmer's) throughout the whole wall of the aorta in this portion, which made it difficult to ascertain whether any of these tears in the intima occurred ante mortem. There was a dissecting aneurysm, filled with fresh blood, which extended from the base of the valve to the beginning of the arch, and involved the anterior and lateral portions of the aortic media. Extravasated blood was present around the adventitia of the intrapericardial portion of the aorta, and especially of the pulmonary artery, where a large amount of blood was extravasated into the adventitia, forming a large hematoma approximately 3 by 2 by 1 cm. The dissection stopped abruptly at the beginning of the arch. Both the arch and descending portion of the aorta



Fig. 3.—Roentgenogram of the left, anterior, oblique view of thorax of M. Van d.P., showing calcified, tortuous aortic arch and descending aorta, and aneurysm and dilatation of the ascending aorta.

showed extreme arteriosclerotic changes, with extensive calcification, forming a rigid, calcareous tube which was very brittle. The circumference of the arch was 8 cm., and that of the descending portion, 7 cm. The intima showed marked arteriosclerosis with numerous ulcerated areas. No mural thrombi were seen. The dissection ended so abruptly when it reached the arch, where the arteriosclerosis was extreme, that it seemed quite possible that the mechanical rigidity halted its course. The splenic and renal arteries were markedly tortuous, calcified, and extremely rigid. Microscopic sections of the ascending portion of the aorta revealed slight to moderate atherosclerosis. The dissection was present in the outer portion of the media, and was composed of recent blood clot. Other sections showed small foci of medial degeneration, with occasional changes suggestive of cyst formation.

Stimulated by these two striking cases, we deemed it of interest to review the autopsy cases of aortic aneurysm at the Massachusetts General Hospital.

Among 9,600 post-mortem examinations which had been done since 1897 at the Massachusetts General Hospital, there were 116 cases of aneurysms of all sorts involving the thoracic and abdominal aorta, or 1.2 per cent of the total number of necropsies. Of this group seventeen were cases of true dissecting aneurysm with *medionecrosis aortae cystica*, and thirteen were cases in which small "dissections" had occurred mostly in and about small atherosclerotic plaques. None of these thirty cases are within the scope of this paper. Of the remaining saccular, fusiform, and cirroid aneurysms, there were eighty-six cases in which the aorta was involved, roughly as follows: twenty-one in the ascending aorta, thirty-seven mainly in the arch, and eight in the descending thoracic portions; there were twenty aneurysms in the abdominal aorta.

Of the sixty-six thoracic aneurysms, sixty were syphilitic and three were definitely arteriosclerotic; in three cases there was marked dilatation of the ascending aorta without arteriosclerosis—a condition we are calling "senile ectasia."

In one of the arteriosclerotic cases (Case 1) and one of the senile ectasia group (Case 2) rupture occurred, as described above in detail.

The two other arteriosclerotic cases may be briefly summarized. One was that of a 70-year-old woman who died of rupture of a dissecting aneurysm of the ascending aorta. At a point about 10 cm. below the aortic arch, just above the diaphragm, there was an ovoid aneurysmal sac about 7 by 5.5 cm., partly filled with old thrombus. There was no communication between this sac and the dissecting aneurysm above; it was regarded as a separate arteriosclerotic aneurysm.

The third case of arteriosclerotic, thoracic, aortic aneurysm was that of a 90-year-old man who died of bronchopneumonia following reduction of a strangulated hernia. Here there was a fusiform, severely arteriosclerotic dilatation of the ascending aorta measuring 9.5 cm. in circumference. Further evidence of its arteriosclerotic nature was the presence of a similar but larger aneurysm of the abdominal aorta.

The second of the two remaining cases of senile ectasia was that of a 67-year-old man who died of acute coronary thrombosis. The ascending aorta was smooth, showed very little atheromatous change, and measured 10 cm. in circumference. Its elasticity was markedly diminished.

The third case* of senile ectasia was one in which the aneurysmal dilatation was so large that it had produced dilatation of the aortic ring and aortic insufficiency, and was considered clinically as syphilitic aortitis with involvement of the aortic valve. The patient was a 70-year-old man who had had dyspnea and palpitation on exertion for many years. He first consulted his physician one week before admission because of dyspnea and edema of the legs. When examined in the emergency ward he was semicomatose. There was marked pulsation of the neck vessels, and a pulsating mass was felt behind the suprasternal notch. The heart was greatly enlarged, and the supracardiac dullness measured 10 cm. There were loud systolic and diastolic murmurs at the base of the heart. The blood pressure

*This case was discussed in detail in the Case Records of the Massachusetts General Hospital, Case 18162, *New England J. Med.* 18: 861, 1932.

was 200/55. The pulse was Corrigan in type, and Duroziez's sign was present. The Hinton test was negative. Post-mortem examination showed a tremendously dilated, inelastic ascending aorta which measured 15 cm. in circumference (Fig. 4). The intima was perfectly smooth, and neither grossly nor microscopically was there any evidence of either syphilis or atherosclerosis.

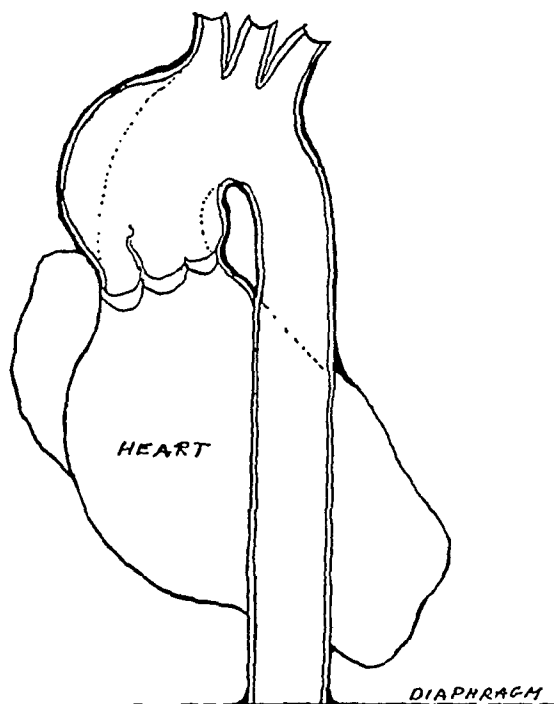


Fig. 4.—Diagram of heart and aorta of a third patient of the present series of senile ectasia (man of 70 years). The dotted lines represent what should be the normal contour of the ascending aorta and the aortic arch.

Of the twenty abdominal aortic aneurysms, only three were syphilitic; the other seventeen were arteriosclerotic. All of the former and six (or one-third) of the latter ruptured. The average age at death in the entire syphilitic group of sixty-three cases was 46.4 years, and in the arteriosclerotic and senile ectasia group of twenty-three cases, 72.7 years (the three patients with senile ectasia averaged 71 years).

DISCUSSION

Since the time of Galen medical interest in arterial aneurysms has been as widespread as the knowledge of the etiologic and pathologic aspects has been vague. Before the discovery of the *Spirochaeta pallida*, most aneurysms, especially the nontraumatic, noncongenital varieties, were thought to be caused by arteriosclerosis. But afterwards, as the disease syphilis became better understood and its pathology widely known, the etiologic pendulum swung to the other extreme. In 1928, MacCallum¹ stated that "true aneurysms are the result of syphilitic disease of the wall of the vessel." Two years later, however, Korns² presented two cases of undoubted atherosclerotic aneurysm of the thoracic aorta which occurred, in each instance, in elderly persons who had

marked atherosclerosis elsewhere in the larger arteries and no serologic or pathologic evidence of syphilis. These cases gave undoubted proof of the etiologic role which atheroma may play in the production of aneurysm. Karsner,³ however, averred in 1938 that only rarely are aortic aneurysms the result of intimal arteriosclerosis except in the abdominal aorta, where it is a cause in a fair number of cases. The relative importance of such aneurysms in the future becomes apparent when one considers, on the one hand, a constantly aging population with its now inevitable increase in atheroma and the consequent increase in the frequency of arteriosclerotic aneurysm, and, on the other hand, a steadily declining incidence of syphilis in the masses.

In discussing the clinical aspects of thoracic aneurysms, Mills and Horton⁴ stated that approximately 85 per cent of thoracic aneurysms are said to be syphilitic, and most of the remaining ones arteriosclerotic. In their series, 70 per cent of the patients (total of 339) had syphilis, and in the remaining 30 per cent there was no history of syphilis or evidence of the disease. In 18 per cent of the latter group, arteriosclerosis of the higher grades ("3 to 4 plus") was present, but they were careful to admit that without suitable anatomic confirmation this association did not permit one to assume that atherosclerosis was the cause of the aneurysm. Because of the advanced age of the patients in the series, it was concluded that arteriosclerosis was probably an etiologic factor in a large number. No anatomic studies were done.

Only a few years ago the clinician considered it an axiom that all large aortic aneurysms were syphilitic in origin; small mycotic or infectious aneurysms were admitted as possibilities to be diagnosed rarely, if ever, during life. Hence, whenever it was obvious clinically or roentgenologically that an aneurysmal dilatation of the aorta was present anywhere, whether in the ascending or descending portions or in the arch, little or no doubt was entertained that the patient had old syphilitic infection, no matter what the history, serologic reaction, sex, or age of the patient might be, or even what the pathologist might have to say.

Meanwhile the pathologist had become convinced, with the passage of time, that, occasionally, large aneurysms of the aorta are not syphilitic in origin, but are arteriosclerotic in nature or of the type of so-called senile ectasia in which a loss of elasticity allows a chronic ballooning out of the ascending aorta, without atheroma or calcification. It is common knowledge, of course, that arteriosclerosis of the aorta is itself precipitated or speeded up by an underlying syphilitic aortitis which may be more or less concealed by the sclerotic process that overlies it, but in the cases with which we are now concerned, no such basis could be discovered by careful search.

Slight to moderate dilatation of the ascending aorta with advancing age is not an uncommon post-mortem finding, and it is usually ex-

plained as the result of a decrease in elasticity. Numerous studies on this subject,⁵⁻⁷ testing the elasticity of both whole aortas and strips of aorta, have all shown that there is a definite diminution of elasticity with the process of senescence. Microscopic examination of sections stained for elastic tissue does not, however, reveal any such change. Elastic fibrils still remain, but it is quite possible that, although they continually take the elastic tissue stain, they have lost their functional elasticity. Recently, Krafka⁸ has shown that 20 per cent of the loss in elasticity of the aorta with age results from fibrosis. The extreme degree of ectasia that was seen in the cases cited, however, is certainly unusual.

Just as in the case of dissecting aneurysms, so too in that of arteriosclerotic aneurysmal sacs, the pathologist was well in advance of the clinician in his knowledge of aortic disease. But he kept this knowledge too much to himself, or we might better say that the clinician did not ask to be instructed. Incidentally, the details of coronary artery disease are perhaps the most glaring example of the slowness with which the pathologist's knowledge penetrated the sickroom. Finally, five or ten years ago, internists began very slowly to learn that abdominal aortic aneurysms might be entirely arteriosclerotic in origin, and, moreover, might rupture and cause rapid death. We are sure that many physicians who are not yet past middle age had no such teaching in their early days in medicine.

And now we realize, from such cases as we have recounted above, that even large *thoracic* aortic aneurysms may be of an arteriosclerotic or senile nature, and that they too may rupture, with fatal hemorrhage.

An important clue to the diagnosis of arteriosclerotic aneurysms and senile ectasia of the thoracic aorta, in some cases at least, is the combination of old age, female sex, and negative serologic reaction. Recognition of this condition and proper diagnosis are of more than academic interest, for neither should such aneurysms stigmatize the patient as syphilitic, nor should the patients receive antisiphilitic therapy, which is a tedious, costly, unnecessary, and, indeed, hazardous procedure in these old people.

There remains to be explained the continuous murmur which was heard over the markedly dilated ascending aorta in the case of the old lady with senile ectasia (Case 2). The systolic and diastolic murmurs which were heard at first in her case are easily explained on the basis of the dilated aorta and stretched aortic valve ring, but the superimposed continuous murmur is not so easily accounted for in the absence of an arteriovenous or interarterial communication, the diagnosis of which was hazarded because of this murmur. Very likely continuous eddies in a large, nonthrombosed sac like this can produce such a murmur, in accordance with the old-fashioned idea.

SUMMARY AND CONCLUSIONS

1. Two case records of elderly women are presented, in which death resulted from rupture of nonsyphilitic aneurysms of the thoracic aorta; one was arteriosclerotic and the other was associated with senile ectasia.

2. Two other cases of arteriosclerotic aneurysm and two more of senile ectasia of the thoracic aorta were discovered on review of the remaining 9,600 autopsy records of the Massachusetts General Hospital. Among these same autopsies there were sixty syphilitic aneurysms of the thoracic aorta, only three syphilitic aneurysms of the abdominal aorta, and twenty-seven arteriosclerotic aneurysms of the abdominal aorta.

3. Middle age (46.4 years) was the average length of life for the syphilitic group, while old age (72.7 years) was the rule when the aneurysms were caused by arteriosclerosis or senile ectasia.

4. As a result of a constantly aging population and a gradual reduction of the incidence of syphilis in the masses, it is postulated that the importance of arteriosclerotic aneurysms and senile ectasia will increase in the coming years, and that these conditions will be more commonly found if more autopsies are performed on aged persons who have hitherto failed to attract interest beyond a customary diagnosis of arteriosclerosis or senility on their death certificates.

REFERENCES

1. MacCallum, W. G.: A Textbook of Pathology, Ed. 4, 1928, p. 750, W. B. Saunders Co., Philadelphia.
2. Korn, H. M.: Über das atherosklerotische und Kombinationsaneurysma, *Virchows Arch. f. path. Anat.* 279: 512, 1930.
3. Karsner, H. T.: Human Pathology. A Textbook, J. B. Lippincott Co., Philadelphia, 1938, p. 481.
4. Mills, J. H., and Horton, B. T.: Clinical Aspects of Aneurysm, *Arch. Int. Med.* 62: 949, 1938.
5. Roy, C. S.: The Elastic Properties of the Arterial Wall, *J. Physiol.* 3: 125, 1880-1882.
6. Hallock, P.: Arterial Elasticity in Man in Relation to Age as Evaluated by the Pulse Wave Velocity Method, *Arch. Int. Med.* 54: 770, 1934.
7. Hallock, P., and Benson, I. C.: Studies on the Elastic Properties of Human Isolated Aorta, *J. Clin. Investigation* 16: 595, 1937.
8. Krafka, J.: Changes in the Elasticity of the Aorta With Age, *Arch. Path.* 29: 303, 1940.

THE NORMAL AND ABNORMAL ESOPHAGEAL
ELECTROCARDIOGRAM, WITH PARTICULAR
REFERENCE TO MYOCARDIAL
INFARCTION

JAN NYBOER, D.Sc., M.D.
NEW YORK, N. Y.

THE concept of the electrical field of the heart in acute coronary disease has been greatly broadened by the use of exploratory precordial leads. The well-known contributions of Wilson, et al.,¹⁻³ and of Wolferth, et al.,⁴⁻⁶ which led to the routine use of the precordial lead, have established the validity of the exploratory method in making a positive diagnosis of anterior myocardial infarction.

Following the work of Lieberman and Liberson⁷ and of Brown,⁸ Hamilton and Nyboer⁹ proposed using an esophageal electrode for localizing and evaluating posterior ventricular infarcts. In the present investigation, cases have been observed in which the onset of coronary occlusion ranged from one day to sixteen years prior to study by the esophageal leads. In these same cases, standard electrocardiograms and exploratory electrocardiograms of each extremity and of several positions on the precordium were also recorded.

Hamilton and Nyboer⁹ and Nyboer¹⁰ showed that the auricular intrinsic waves of Lewis were present in the P waves which were recorded from the auricular level and absent in those recorded below and above the auricular level. It was possible, therefore, when the pacemaker was in the region of the sinus node, to differentiate electrocardiograms from the left auricular and left ventricular levels by taking serial esophageal leads at 2.5 cm. steps between the lowest and highest levels. P waves were selected from esophageal electrocardiograms which usually resembled those in standard Leads I and II, without intrinsic deflections, and the ventricular levels were ascertained from multiple esophageal leads on normal and abnormal subjects. An attempt was made to show that the esophageal electrocardiogram from the ventricles is as specifically diagnostic of posterior myocardial infarction as the precordial electrocardiogram is diagnostic of anterior wall infarction.

From the Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University, New York City.

Presented as a preliminary report at the meeting of the New York Heart Association, New York Academy of Medicine, Jan. 24, 1939.

This investigation was made possible by funds provided by the Cardiac Committee of the New York Post-Graduate Medical School and Hospital.

Received for publication Jan. 18, 1941.

It will also be shown that the criteria for a diagnosis of posterior myocardial infarction by the esophageal ventricular lead are essentially the same as those employed for a diagnosis of anterior myocardial infarction in the precordial lead.

NOMENCLATURE AND METHOD

The standard leads were marked I, II, and III. A selected precordial lead, marked IV, was taken from the region of the apex, or V_4 to V_6 region of Wilson. The selected juxtaventricular lead in the esophagus was marked EV, and hereafter will be referred to as "EV lead." The selected juxta-auricular lead in the esophagus was marked EA, and will be referred to as "EA lead." The esophageal tracings were usually perforated with the distance in centimeters from the nares or incisor teeth to the retrocardiac exploratory level. The limited or selected leads were used in order to illustrate the more significant observations with relation to the anterior and posterior wall of the heart, although complete data were available in each case.

The central terminal of Wilson, Johnston, Macleod, and Barker was used as the indifferent electrode in the precordial, extremity, and esophageal leads. All exploratory leads were recorded in such a way that an electronegative deflection was a downward movement on the graph, and thus they conform to the new terminology for exploratory electrocardiograms recommended by the American and British Heart Associations. The usual level for study of the posterior part of the heart ranged between 30 and 60 cm. from the incisor teeth or nares. The patient was usually in the recumbent position while the esophageal ventricular leads were being recorded. This was helpful in probably preventing excessive overlapping of the left auricle over the left ventricle, which would have confused the electrical picture in this region.

Since the roentgenkymographic studies of Gubner and Crawford¹¹ on coronary thrombosis appeared simple and diagnostic, it seemed that their method might possibly be used as a check on the validity of the esophageal electrocardiogram. Hence, a No. 14 soft rubber tube was equipped with a whalebone insert upon which radiopaque metal rings were mounted and properly spaced. This esophageal tube was used to identify the posterior levels of the heart in the conventional or kymographic roentgenograms. The observations in two cases of typical posterior myocardial infarction will be presented by this method; the records were made with the patient in the standing position.

RESULTS

A. The Normal Esophageal Lead

In each of four normal subjects (D. B., aged 22, E. G., aged 26, and D. K., aged 40, in Fig. 1, and R. W., aged 26, in Fig. 2) a close resemblance was noted between the potentials of the selected Lead IV and the EV lead, in spite of minor deviations in electrical axis as shown in the standard leads. At the esophageal auricular level the QRS complex and the T wave were usually approximately inverted images of the normal ventricular potentials in the apical and esophageal ventricular leads. P in Lead EA showed intrinsic waves which were easily identified at several levels.

In each EV lead the P waves showed no evidence of intrinsic deflections, and were usually smooth, convex, and upright. The ventricular complex was usually composed chiefly of an R wave. A small Q wave was rarely present, and was not considered abnormal clinically unless it exceeded 0.4 millivolt, and was present with other abnormalities. The S wave could normally be absent. The RS-T segment was approximately isoelectric. The T wave was usually convex, upright, and definitely electropositive in all normals. Deviations from these findings were considered abnormal in the following cases.

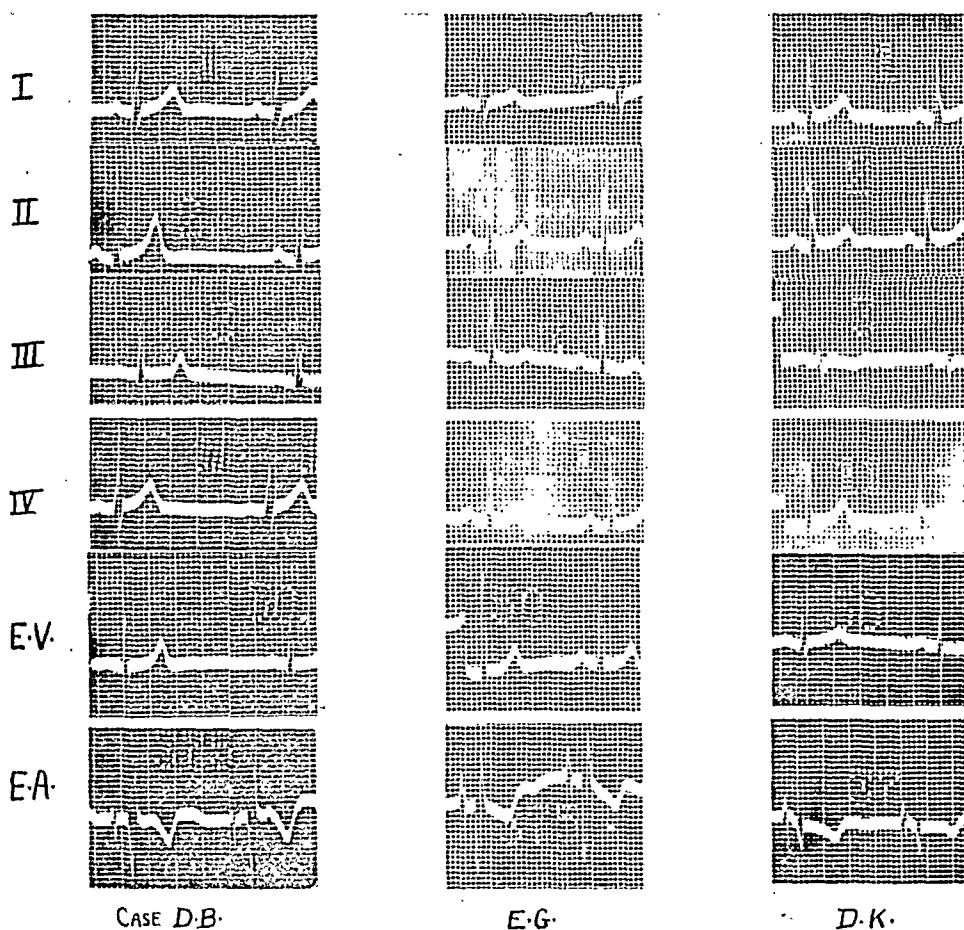


Fig. 1.—Standard, precordial, and esophageal electrocardiograms on three normal subjects, showing the close similarity between Lead IV and Lead EV. Note that the QRST deflections in EA are essentially inverted images of QRST in EV and QRST₄.

B. Anterior Myocardial Infarction

B. C. (a man, aged 49), previously cited by Hamilton and Nyboer,⁹ showed abnormalities in the standard and fourth leads, which, together with a typical clinical history and course, appeared sufficient for a diagnosis of anterior myocardial infarction. Six weeks after the onset of the disease, the precordial lead (Fig. 2) showed an abnormal Q as the sole QRS complex, and a sharply inverted T wave. These abnor-

malities, together with the progressive change observed previously, were diagnostic of anterior myocardial infarction.

The EV potentials in this case resembled the esophageal ventricular potentials of normal subjects; however, minor abnormalities of the RS-T segments and T waves were present. The EA potentials were markedly abnormal in this case; the initial and final ventricular complexes were essentially inverted images of potentials from the precordium over the "central area" of infarction (Fig. 2).

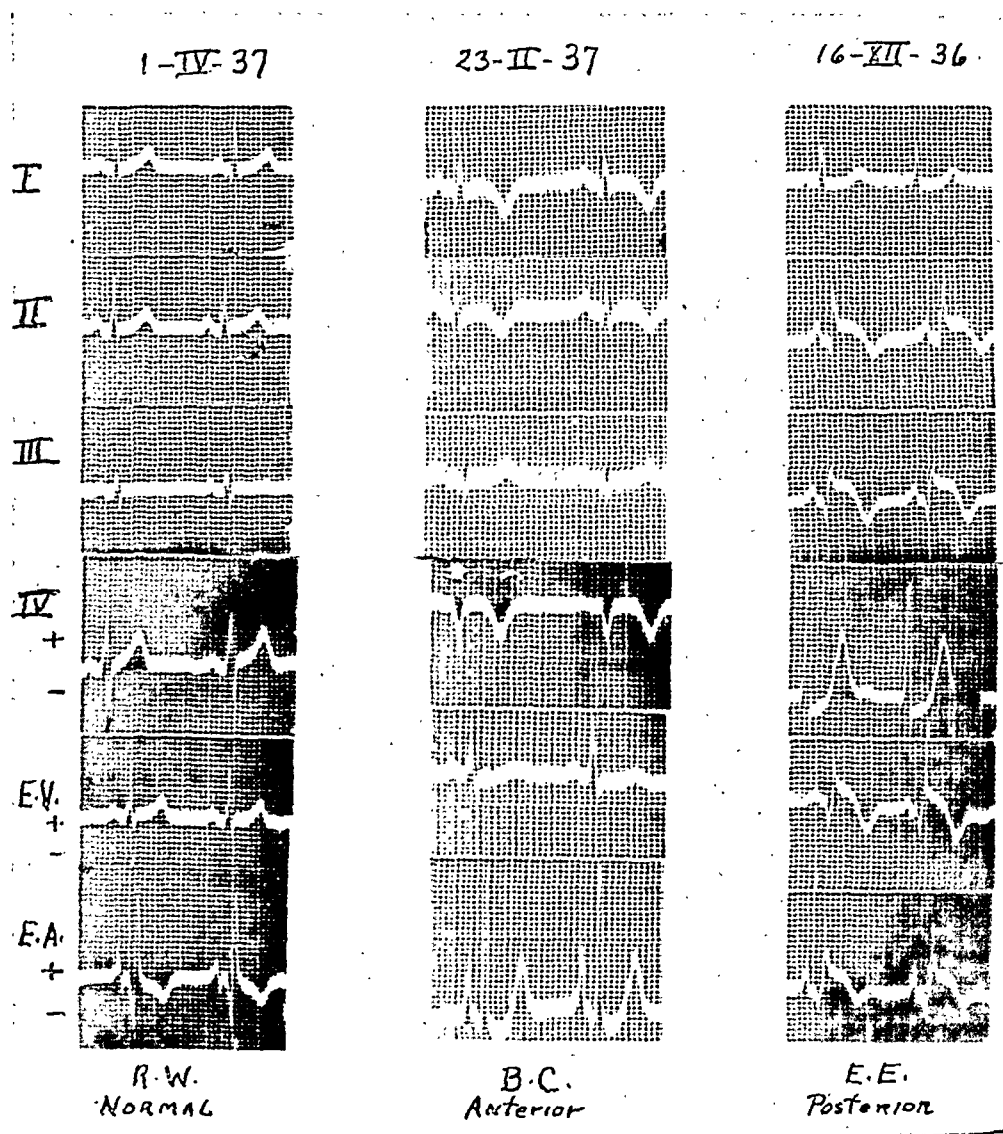


Fig. 2.—Comparison of tracings from a normal subject with those in cases of anterior and posterior coronary occlusion, using standard and selected exploratory leads. (These tracings were modified and reprinted by permission of the authors, Hamilton and Nyboer⁹.)

C. Recent and Healing Posterior Myocardial Infarction

CASE 1.—E. E., a man, aged 59, previously cited by Hamilton and Nyboer,⁹ suffered a typical attack of coronary occlusion. The usual four leads supported the clinical diagnosis and indicated that the occlusion was a posterior one (Q₃T₃ type).

One day after the onset of the disease, the EV potentials resembled Lead III (Fig. 2) and the left leg extremity potential (not shown). The authors commented that these curves were comparable to those which are obtained at the margin of experimental infarcts, as shown by Wilson and his collaborators,³ and that the infarct probably did not involve the entire thickness of the muscle under the electrode. In esophageal Lead EV the Q wave was about one-third the size of the QRS, and was associated with a markedly elevated RS-T segment and inverted T wave. The juxta-auricular leads were also abnormal and showed a small Q wave, a tall R wave, an elevated RS-T segment, and a diphasic T wave.

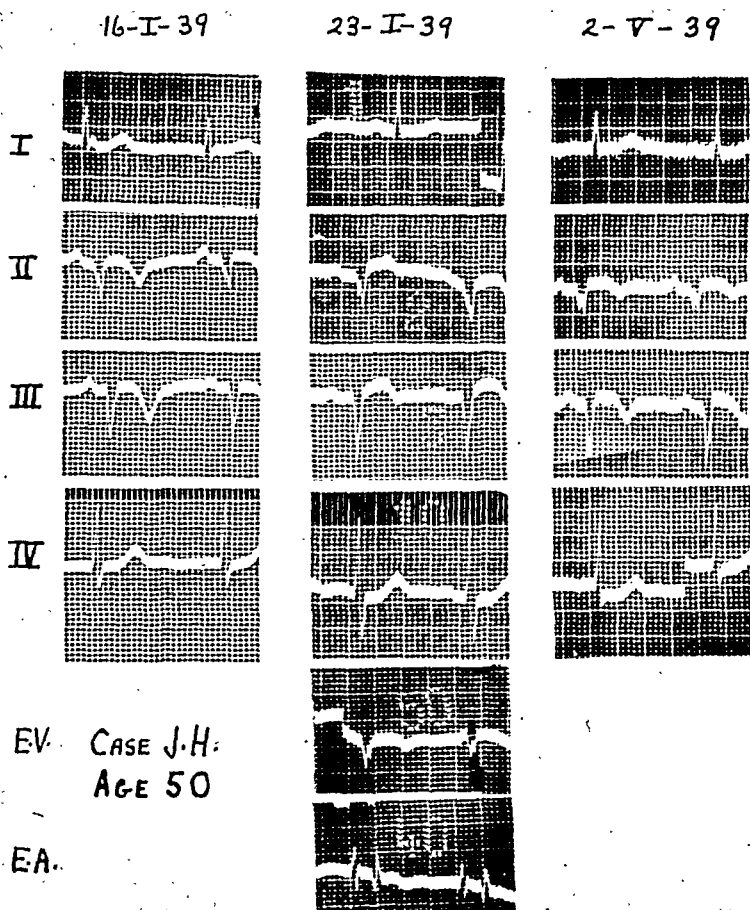


Fig. 3.—Three electrocardiograms on a patient with posterior coronary occlusion, showing an abnormal Q in EV as the sole QRS deflection, accompanied by inversion of T in EV.

CASE 2.—J. H., a man, aged 50, had a typical attack of coronary occlusion while at work (January 14). A few hours later this diagnosis was confirmed by a four-lead electrocardiogram in his physician's office, and the patient was hospitalized. On the third hospital day, January 16, a tracing of the Q_3T_3 (Fig. 3) type indicated that the occlusion was posterior, but Lead IV was not definitely abnormal.

On the ninth hospital day, January 23, esophageal lead EV (Fig. 3) showed a Q wave as the sole QRS deflection, an inverted T wave, and an isoelectric RS-T segment. The corrected Q wave measured 1.5 millivolts, and the T wave was negative by 0.3 millivolt. The EA lead was not definitely abnormal. Thus the progressive and marked RS-T and T-wave changes in the standard leads, with the persistently abnormal Q_2 and Q_3 , established the correctness of the diagnosis of posterior myocardial infarction; this was also supported by the EV lead changes.

A four-lead electrocardiogram on May 2 (Fig. 3), taken two days after the second attack of coronary occlusion and 3.5 months after the first occlusion, suggested the possibility of a superimposed, recent, posterior myocardial infarction. The patient died on May 3. Necropsy was not permitted.

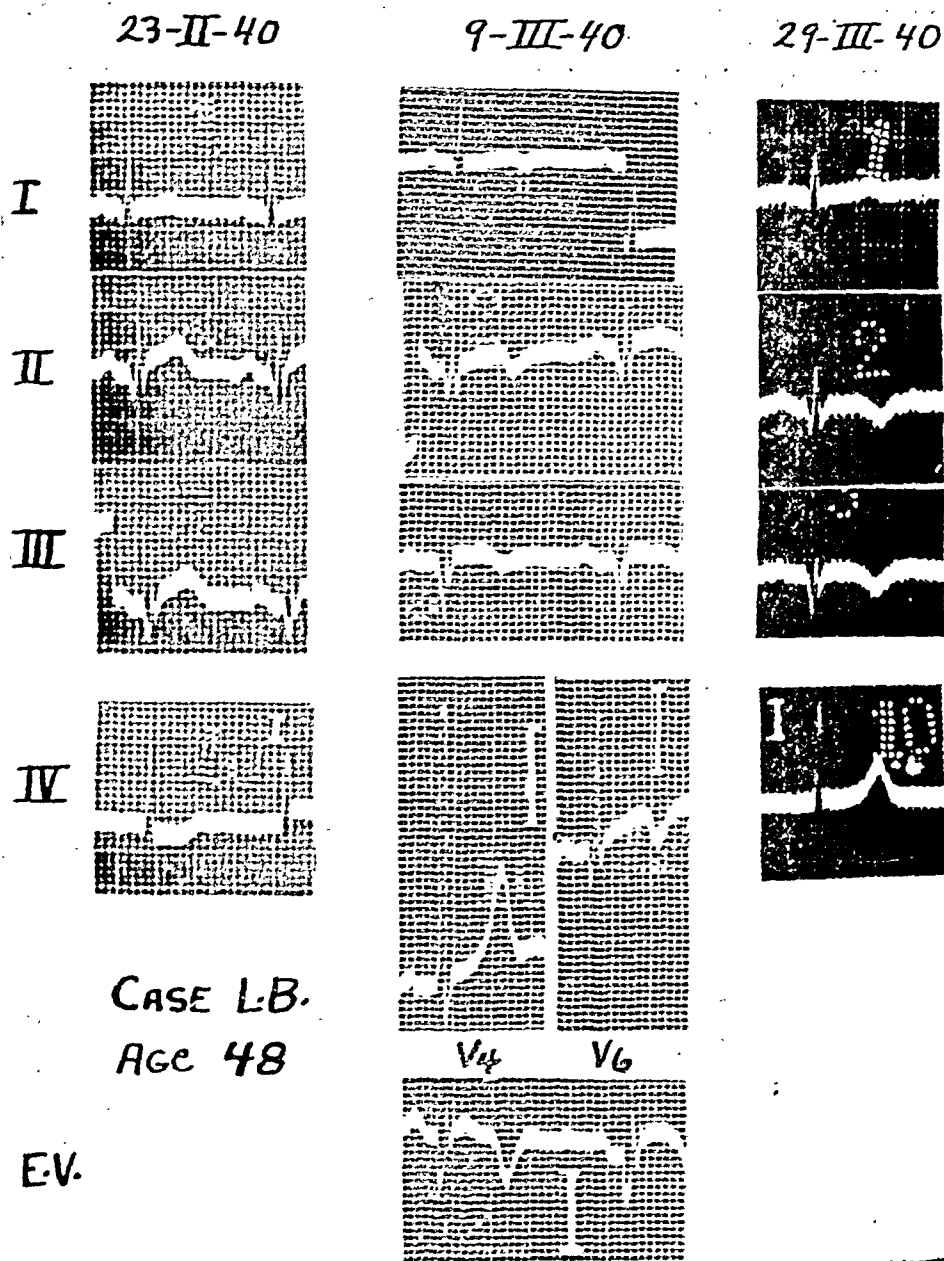


Fig. 4.—Three electrocardiograms on a patient with coronary occlusion, showing abnormalities in the EV lead which indicate that the myocardial infarct is posterior. (Variations in the standardization of the EV lead and Lead IV are indicated by the vertical white lines.)

CASE 3.—L. B., a man, aged 48, was well until two months before admission to this hospital, when he first complained of intermittent "indigestion." About one week before entry he had suffered from acute, localized, precordial distress without radiation; it lasted a few hours and was relieved by a "hypodermic injection." An electrocardiogram taken a few days later was said to have been abnormal; the industrial physician, however, permitted him to return to work the same week.

One day before entry he had a second, severe attack of precordial distress which was not relieved by 5 nitroglycerine tablets. It persisted for about four hours.

A four-lead electrocardiogram on admission (Fig. 4, February 23) showed an abnormal Q_2 and Q_3 , an elevated $RS-T_2$ and $RS-T_3$, a depressed $RS-T_4$, and an upright T_2 and T_3 . These abnormalities, together with progressive changes in the next twenty-four hours and the history, were adequate to establish a diagnosis of very recent myocardial infarction involving mainly the posterior ventricular wall. The precordial series (Fig. 4, March 9) showed an essentially normal V_4 , but an abnormal V_6 , which was probably indicative of an associated, incomplete infarction of the apex. Additional, progressive, standard lead changes were apparent on March 29 (Fig. 4).

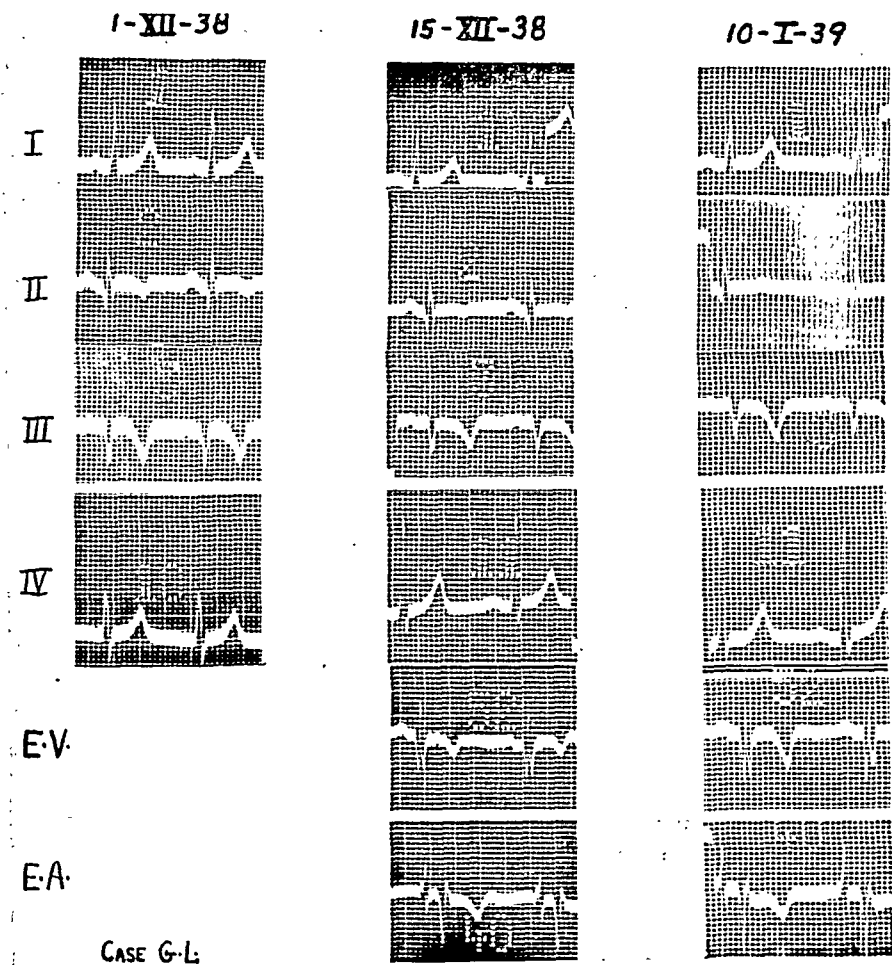


Fig. 5.—Three electrocardiograms on a patient with posterior myocardial infarction, showing persistence of the EV abnormalities after a three-week interval.

Esophageal Lead EV (Fig. 4, March 9), about three weeks after the onset of acute symptoms, showed an abnormal Q of 0.6 millivolt, and greater, from several levels, followed by a small R summit, a small S, a slightly elevated $RS-T$ segment, and a moderately inverted T wave. No satisfactory EA leads were recorded; the abnormal EV lead, however, confirmed the suspicion of posterior myocardial infarction which was aroused by the changes in the standard leads.

CASE 4.—G. L., a man, aged 43, had a typical history of coronary occlusion in October, 1938. About one month later, Dec. 1, 1938, the (four lead) electrocardiogram (Fig. 5) showed conclusively that the patient had recently had posterior myocardial infarction.

In the seventh week of the disease, esophageal Lead EV, with the electrode 52.5 cm. from the nares, showed a deep Q wave of 0.6 millivolt, followed by a smaller R wave and an S wave which was equivalent in voltage to the Q wave, an isoelectric RS-T segment, and a sharply inverted T wave. The EA leads were normal. In the tenth week of the disease, the standard precordial and esophageal leads showed definite changes, as compared with the previous tracings (Fig. 5). The persistent abnormality in esophageal Lead EV at 52.5 cm. was the presence of deep Q waves of 0.8 millivolt, with sharply inverted T waves of 0.6 millivolt. Thus, the changes in the EV lead again confirmed the impression gained from the standard leads. This patient returned to work and has no cardiac complaints.

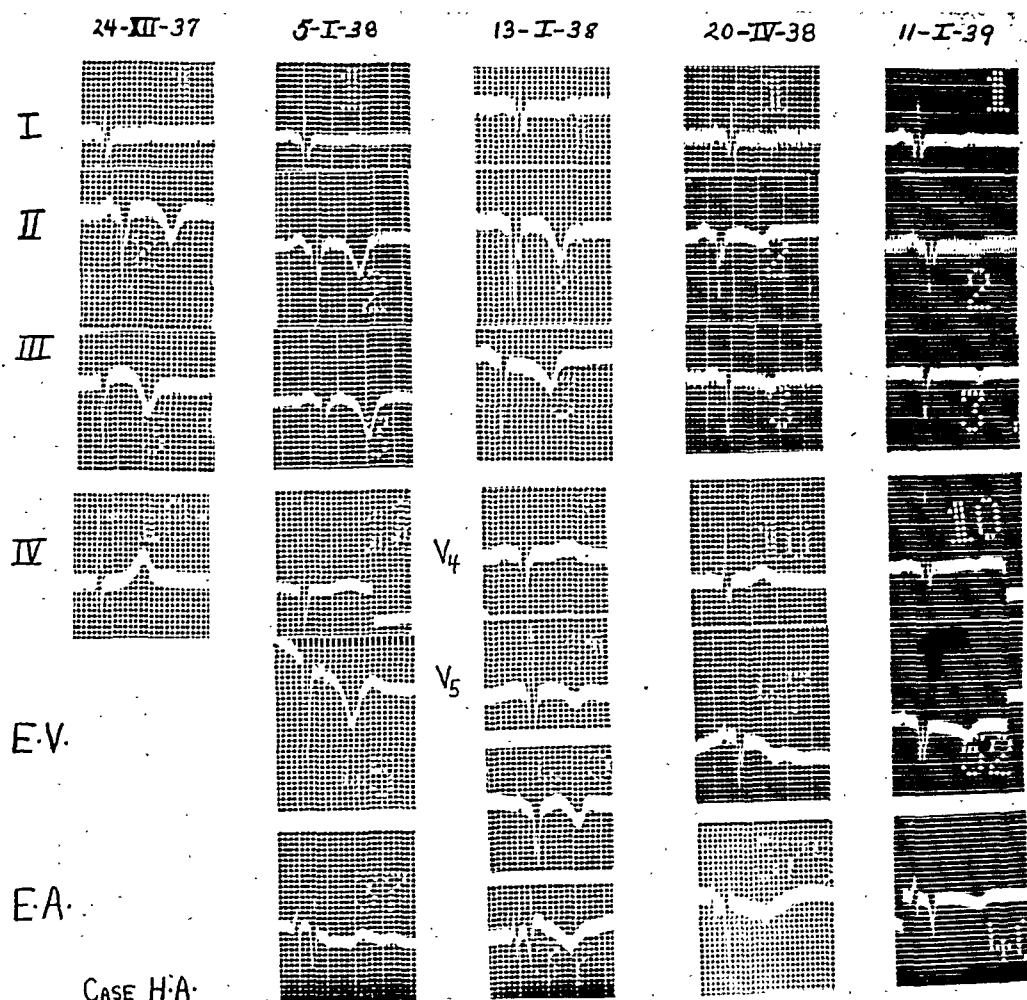


Fig. 6.—Five electrocardiograms on the same patient over a period of one year, showing progressive changes in four EV leads which are indicative of healing of a posterolateral myocardial infarct.

CASE 5.—H. A., a man, aged 58, had an atypical attack of coronary occlusion two weeks prior to admission. The final diagnosis was established on the basis of progressive changes in three routine serial electrocardiograms, in which the Q_3T_3 type of abnormality was ascribed to a posterior myocardial infarction (Fig. 6).

The abnormal, W-shaped QRS₃, with a slightly depressed RS-T₁ segment and a low T₁ of 0.5 millivolt, was explained by the abnormal precordial potentials from the region of the apex; these explorations suggested (Fig. 6, Jan. 13, 1938) that there was an incomplete infarction of the left lateral ventricular wall or apex.

In the fifth week of the disease (Jan. 5, 1938), esophageal Lead EV, with the electrode about 45 cm. from the incisors, showed a deep Q wave only, and a sharply inverted T wave. The EA lead was not definitely abnormal at this time or subsequently, in the course of a year. Abnormal EV potentials were found in this case in the sixth week, and in the fifth, ninth, and eleventh months after the onset of the disease (Fig. 6). All of these confirmed each other, although progressive changes had taken place, presumably because of healing of the infarcted area near the exploratory electrode. It should be noted that, in Lead EV, a persistent, abnormally deep Q wave and inverted T wave remained in this region and at lower levels over this period of time and confirmed the diagnosis of infarction of the posterior ventricular wall which was made from the standard leads.

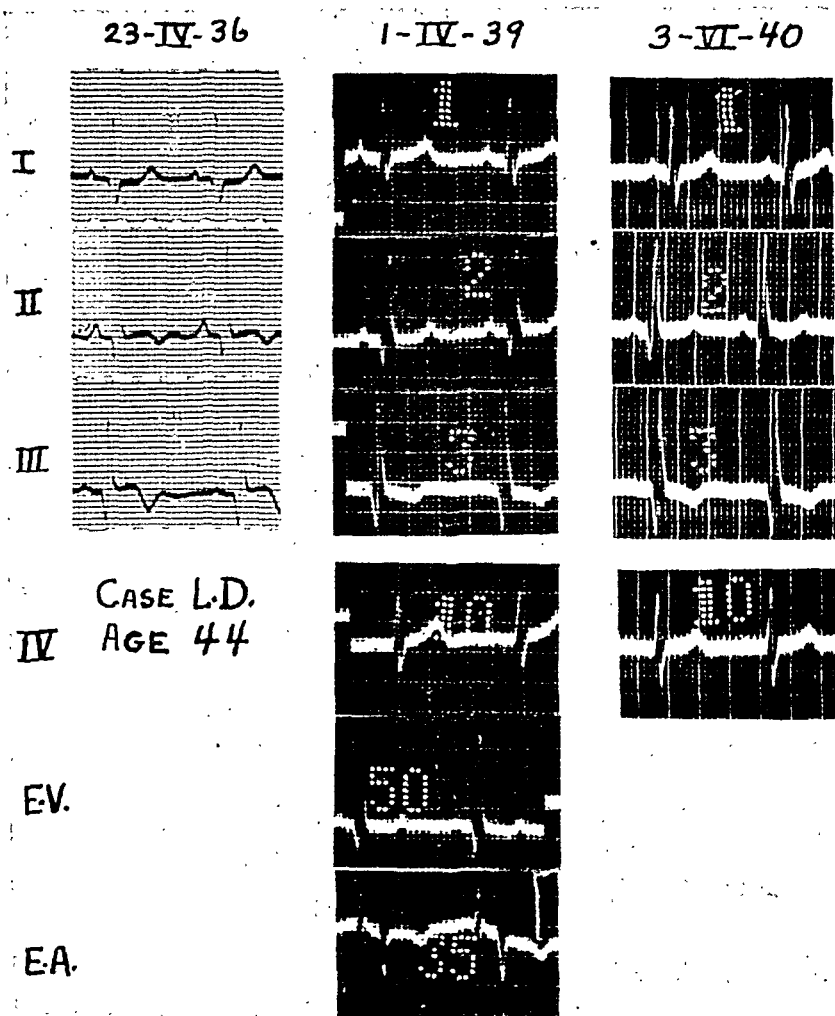


Fig. 7.—Three electrocardiograms on a patient with posterior myocardial infarction, showing progressive changes. Note that the EV lead shows an upright, electropositive T wave.

D. Healed Posterior Myocardial Infarction

CASE 1.—L. D., a man, aged 44, had an attack of coronary occlusion on April 18, 1936. The pain soon disappeared, but dyspnea on exertion continued for about three years. This was relieved by a reduction in weight. In 1940, there were no cardiac complaints. Standard electrocardiograms taken two and five days (Fig. 7) after the onset showed a Q_2T_2 pattern, with progressive changes indicating

recent posterior myocardial infarction. Studies in our laboratory, in 1939, showed a marked tendency for the T wave to return to normal. However, the deep Q_2 and Q_3 persisted. One year later, no evidence of further change in the standard leads could be detected. Lead IV was normal in 1939 and 1940.

The EV leads (Fig. 7, April 1, 1939), taken three years after the initial symptoms, showed an abnormal Q wave, 0.7 millivolt in size, or larger, from levels 45.0 to 55.0 cm. from the nares. This was associated with tall R waves and upright T waves at each level. However, the EA leads were within normal limits. It appears that in the EV leads the T waves may be upright if healing of the posterior infarct has taken place.

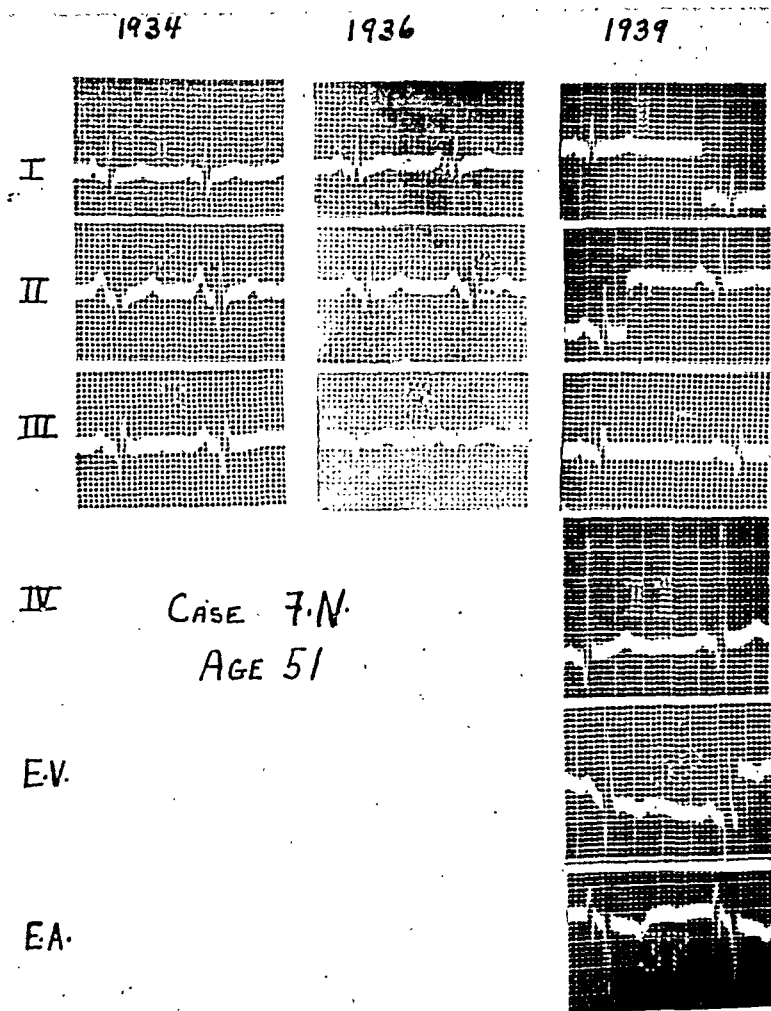


Fig. 8.—Three electrocardiograms on the same patient, showing that the EV lead is helpful in the interpretation of borderline electrocardiograms from Lead III.

CASE 2.—F. N., a man, aged 51, was first studied in the cardiac clinic in 1934, when he complained of anginal attacks which were related mainly to exertion, lasted from one minute to several hours, and had occurred intermittently during the preceding two years. The patient stated in 1939 that, three or four months prior to examination in 1934, he had had a severe attack of distressing precordial pain of twenty-four hours' duration, accompanied by a cold sweat. Morphine was required to arrest the pain. After this attack the angina had diminished considerably. Thus, clinically, he had arteriosclerotic heart disease associated with a persistent anginal syndrome, and had probably had a coronary occlusion in 1939.

In the first electrocardiograms (Fig. 8), taken in 1934 and 1936, attention was drawn to deep Q waves in Leads I, II, and III of 0.2 millivolt and greater. They were never regarded as being caused by coronary occlusion, probably because the conventional inversion of the T waves in Leads I, II, and III had not occurred in the tracings. In comparison with the 1939 tracings (Fig. 8), little change except the slight regression of the T waves in Leads I, II, and III had taken place. In the precordial series at this time, Q waves of 0.4 millivolt were present, with positive T waves in the V_5 to V_6 region. Unless additional evidence were forthcoming, these observations would be equivocal in so far as the possibility of myocardial infarction was concerned.

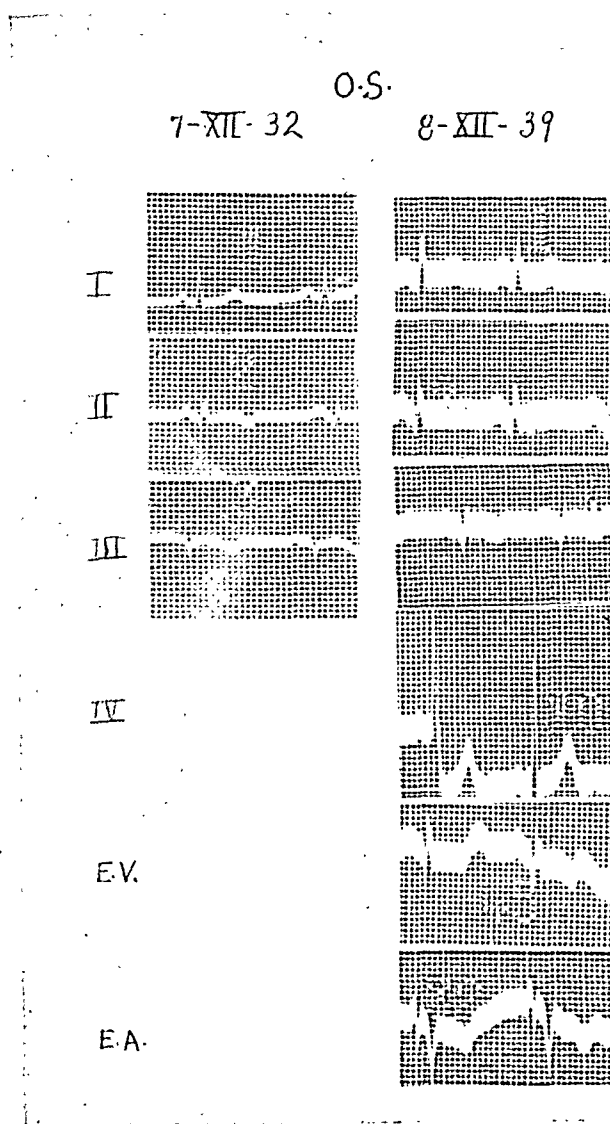


Fig. 9.—Two electrocardiograms on the same patient, showing that the EV lead and Lead IV are helpful in interpreting low voltage electrocardiograms; the patient had no complaints referable to his heart at that time.

In 1939, about five years after the onset of the disease, the EV leads from several levels were abnormal. The EV lead at 52.5 cm. (Fig. 8, 1939) showed a deep Q wave of 0.7 millivolt, associated with a slurred R wave of 1.2 millivolts and an inverted T wave of 0.13 millivolt. The EA leads were within normal limits. Thus,

myocardial infarction which was not clearly indicated by the standard leads was diagnosed by means of an abnormal esophageal electrocardiogram about five years after its occurrence.

CASE 3.—O. S., a man, aged 52, was studied in the cardiac clinic for the first time in 1932. He complained of intermittent chest pain, with radiation down the left arm, which was related to physical exertion. There was no history of an acute onset. He was well developed, somewhat obese, and weighed 190 pounds. Although he was not cooperative in the clinic, he later returned voluntarily for an electrocardiogram. At this time he no longer had angina, and was working steadily at the age of 59. He had not reduced his weight. Clinically, in 1939, the case was one of asymptomatic or healed coronary occlusion. The initial electrocardiogram (Fig 9, 1932) was of the Q_3T_3 type, with low voltage, and was typical of posterior myocardial infarction. The standard leads, in 1939, showed a persistent Q_3T_3 pattern, with T-wave changes toward a more normal direction, but of low voltage. Lead IV was within normal limits.

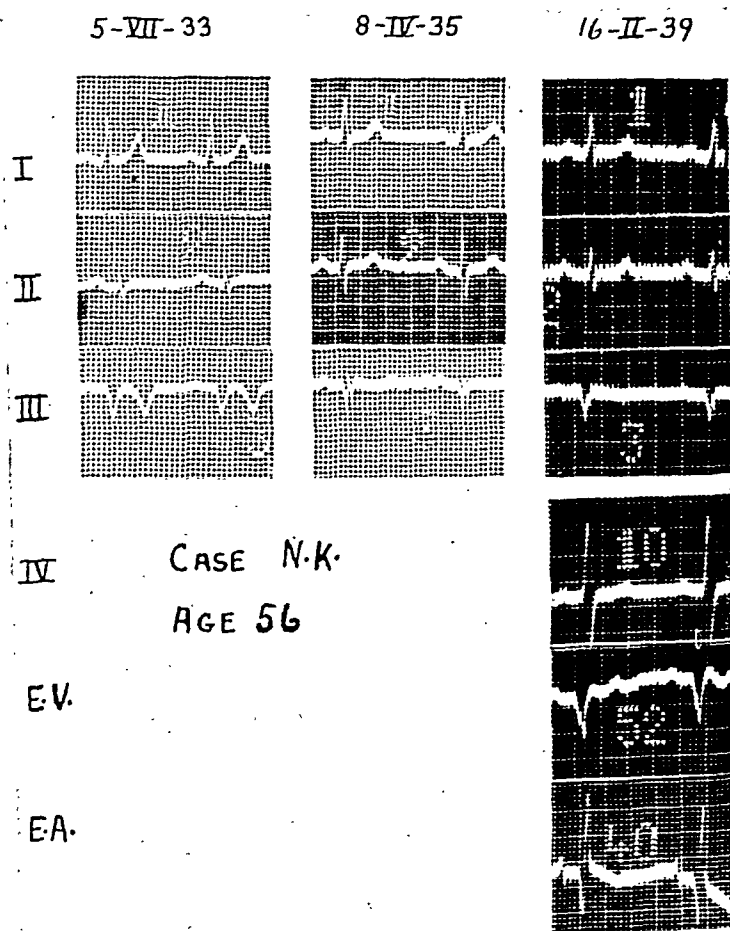


Fig. 10.—Three electrocardiograms on a patient with posterior myocardial infarction, showing an upright T wave in Lead EV in the healed stage of the disease, six years after the initial symptoms.

About seven years after the initial signs of coronary disease, the EV leads (Fig. 9) showed a Q wave of 0.7 millivolt and a diphasic T wave, which were definitely abnormal. The deep Q wave was present from 45 to 57.5 cm. from the nares, and at lower depths it was associated with an inverted T wave. The EA leads were within normal limits.

CASE 4.—N. K., a man, aged 56, suffered severe precordial distress while at work two months prior to his first clinic visit on June 29, 1933. This was not relieved by stooping over, and the patient was forced to take a taxicab home, although he had walked forty blocks to work on the same day. He remained in bed for about three months. This story, together with changing electrocardiograms (Fig 10), probably of the Q_sT_s pattern, accompanied by low voltage of QRS_2 was, in 1933, adequate to establish a diagnosis of posterior myocardial infarction. Five years after the initial symptoms, although the patient had no complaints referable to the heart, Q_s was still the sole QRS_s complex; however a significant Q_2 was never present.

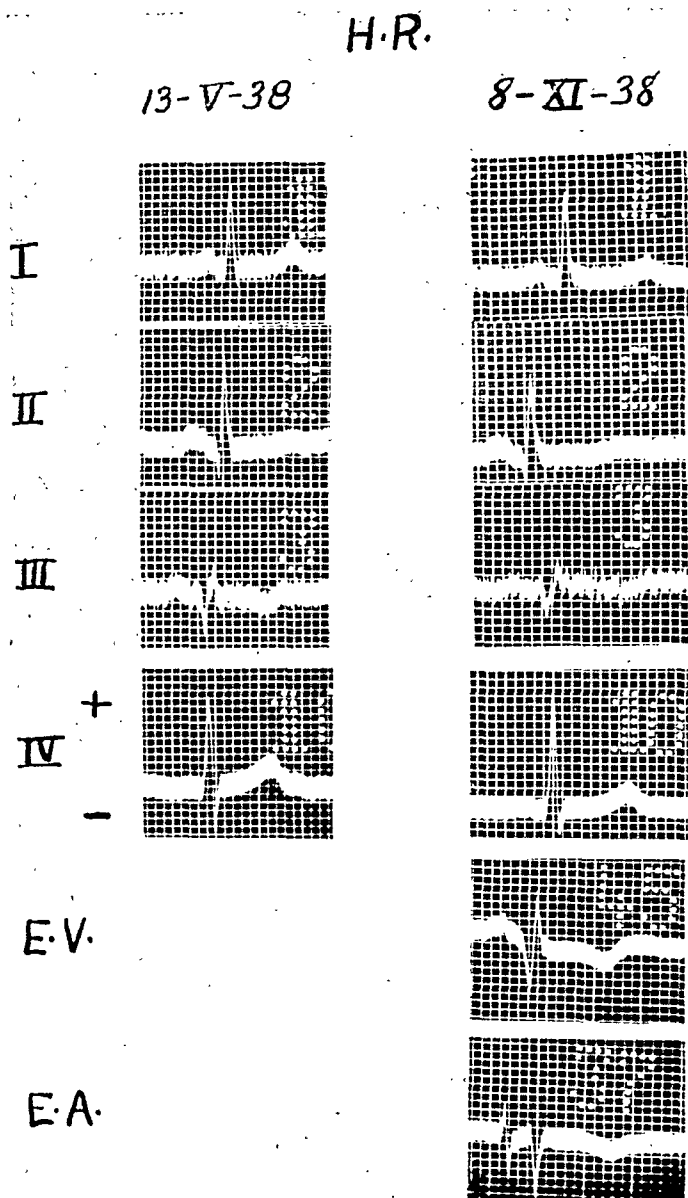


Fig. 11.—Two electrocardiograms on the same patient as in Fig. 12, showing the value of the EV lead in interpreting borderline electrocardiograms sixteen years after the initial symptoms.

The initial EV leads (Fig. 10) at several levels showed only a deep Q of 1.5 millivolts and a positive T wave. The QRS was definitely abnormal, although T was

upright but of low voltage. These abnormalities indicated a posterior wall lesion. Lead EA was within normal limits.

CASE 5 (*A Case of Equivocal Standard Leads*).—A cardiac clinic patient, H. R., a man, aged 73, was in good health in 1938, and had no complaints referable to his heart. As a matter of routine, an electrocardiogram was taken and compared with one made in 1933, which was regarded as normal in our laboratory. However, in the absence of clinical notes, the interpretation of the 1938 record (Fig. 11) stated that the Q_2 and Q_3 were difficult to evaluate, for the voltage of Q_3 was greater than one-quarter of that of R_2 , while T_1 was low and T_3 inverted. Lead IV was normal, and there were no evident changes since 1933 in the standard leads.

In 1939, a history of viselike precordial pain which occurred intermittently for five or six weeks in 1922 was obtained, and it was discovered that initially his complaint had been diagnosed and treated as "influenza" by a private physician. Six weeks later he had come to the cardiac clinic, where his complaints were regarded as indicating "rheumatic fever," with symptomatic myocarditis. Pathognomonic signs of rheumatic heart disease never developed. In 1933, the cardiac diagnosis was changed to "coronary sclerosis associated with a mild anginal syndrome."

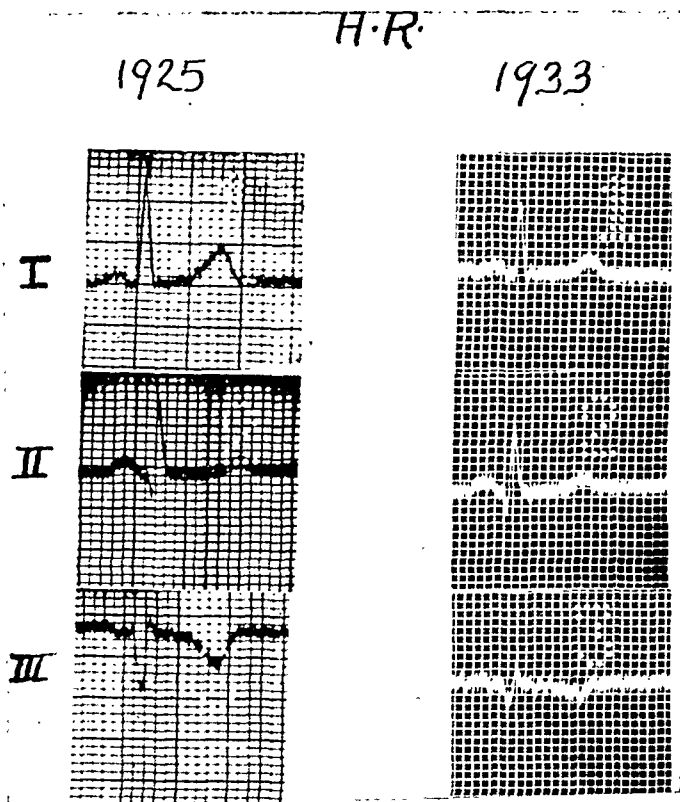


Fig. 12.—Two electrocardiograms on the same patient as in Fig. 11, confirming a late diagnosis of posterior myocardial infarction by the abnormalities in the standard leads.

This history made us skeptical of the earlier diagnosis, and, therefore, the posterior ventricular region was explored on Nov. 8, 1938 (Fig. 11). The EV leads resembled those in the above-described cases of posterior myocardial infarction, and suggested that the patient had a healed posterior myocardial infarct. Sixteen years after the onset of the disease he had a deep Q and inverted T in the EV leads. This diagnosis was later confirmed by the discovery of a deteriorated record which had been taken on this patient in 1925 (Fig. 12). Comparison with more recent tracings (1933, Fig. 12) showed that myocardial changes must have taken

place; in these the abnormal Q_2 and Q_3 were accompanied by a low, upright T_2 and an inverted T_3 . Therefore, the esophageal electrocardiograms led to the specific localization of an old infarct, although the standard leads had been equivocal for the preceding five years.

E. Roentgenkymograms in Posterior Myocardial Infarction

Autopsies were not done in the case of E. E. (Fig. 2) and J. H. (Fig. 3); therefore, there was no opportunity to correlate post-mortem observations with the potentials of the EV leads in cases of posterior occlusion.

Up to the present time, no correlation is known to have been established "in vivo" between the EV lead and the roentgenkymogram in cases of posterior myocardial infarction. This was attempted in two typical cases; however, the EV leads were made with the patients recumbent, and the kymograms with the patients in the vertical position. Therefore, the true kymographic outline of the posterior heart wall may have been obscured by the lower border of the left auricle, for the latter possibly assumes a lower position because of its own weight, or becomes less distorted because it no longer lies in juxtaposition to the spine. This possibility was suggested by comparative studies (not yet reported) of the EA and EV leads in the recumbent and standing positions.

CASE 1.—In the case of G. L. (Fig. 5), which was typical of posterior myocardial infarction, as far as the standard and EV leads were concerned, there was no evidence of infarction in the left lateral kymogram at a level corresponding to 47 to 55 cm. from the nares, which was the location of the infarct, according to the esophageal leads.

CASE 2.—In the case of H. A. (Fig. 6), which was typical of posterior myocardial infarction and incomplete infarction of the left wall, as shown by the standard, precordial, and EV leads, a left lateral roentgenogram and several left oblique kymograms showed no evidence of infarction at levels corresponding to 45 cm. or more from the teeth.

In conclusion, roentgenkymographic studies in these two cases yielded nothing to support a diagnosis of posterior myocardial infarction. It is believed that better results may possibly be obtained by taking roentgenkymograms with the patient in the recumbent position. The negative results in these cases do not rule out infarction of the posterior, lateral, or diaphragmatic cardiac wall.

F. Other Factors Influencing the Initial QRS Deflections in the Esophageal Ventricular Lead

If Q is the only QRS deflection in EV leads, a diagnosis of posterior myocardial infarction is not always justified. This is illustrated by some of the following cases in which there was no evidence of coronary occlusion. The presence of an initial, small R wave in the EV leads is probably not abnormal.

CASE 1 (*Left Axis Deviation*).—H. H., a man, aged 65, had been in good health; his blood pressure was normal, but he had slight cardiac enlargement and a systolic murmur. His electrocardiogram (Fig. 13) showed left axis deviation, a low T_1 , and a normal Lead IV. The EV leads from several levels showed an initial, small R wave of about 0.4 millivolt, and a much deeper S wave. These are not definitely abnormal. The EA leads were within normal limits. This study was done as a routine, not because of complaints, and indicated that caution in the interpretation of the small R wave in EV leads in some cases of axis deviation is necessary.

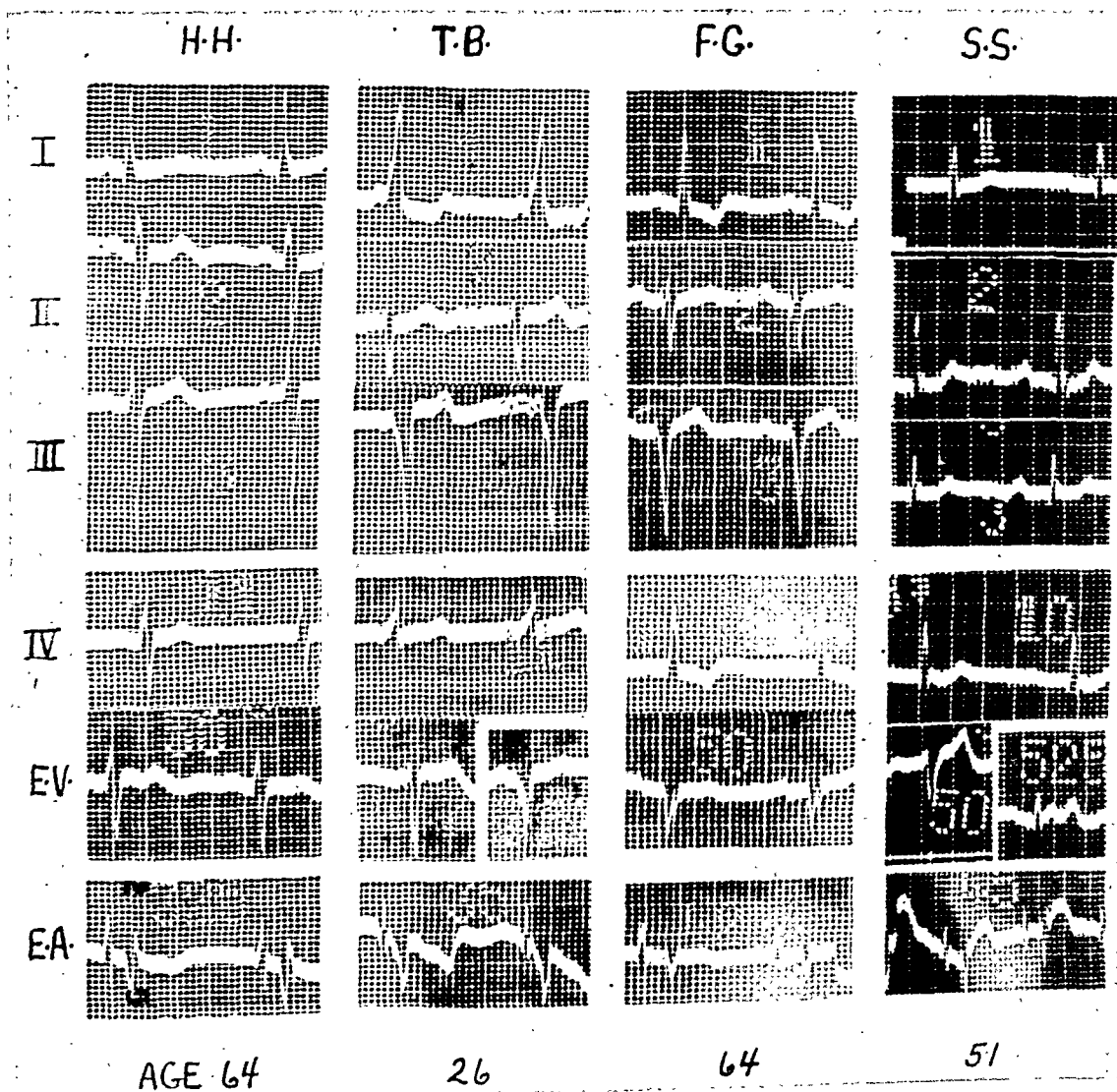


Fig. 13.—Factors influencing the appearance of the QRS complex in the EV leads of four patients, in the absence of a conclusive history or other specific signs of coronary occlusion.

CASE 2 (*Intraventricular Block With Short P-R Interval*).—T. B., a woman, aged 26, had had several short paroxysms of tachycardia during emotion or excessive physical exertion. There was no history of rheumatic fever and chorea, but she had had scarlet fever. There were many ventricular and auricular extrasystoles at the ages of 14 and 16, and murmurs were "intermittent" in childhood. A faint systolic murmur was present in 1939. No roentgenologic evidence of cardiac abnormality was found at any time.

Routine electrocardiograms (Fig. 13) showed a persistently short P-R interval (0.10 second), a prolonged QRS interval (0.12 second), QRS slurring in Leads I, II, III, and IV, marked left axis deviation, and an inverted T_1 . Persistent left axis deviation and intraventricular block, with a short P-R interval, had been present in repeated tracings for the preceding eight years.

The abnormal EV leads (Fig. 13) at the lowest levels (52.5 and 55 cm. from the nares, i.e., probably subdiaphragmatic and in the stomach) showed a slurred Q wave as the sole QRS complex, followed by an isoelectric RS-T segment and upright T wave. At levels nearer the auriculoventricular border (EV, 47 cm.) a small R wave preceded the deep S wave, and was followed by an isoelectric RS-T segment and an upright T wave. The EA leads were not definitely abnormal except for the slurred Q wave, which was the only QRS complex. It was followed by an inverted T wave. In summary, what was apparently a Q wave was present in the EV lead in the absence of coronary occlusion.

CASE 3 (*Left Axis Deviation and Left Ventricular Hypertrophy Associated With Hypertension*).—F. G., a man, aged 64, who was known to have hypertensive cardiac disease, with marked left ventricular enlargement, was admitted to the hospital because of cardiac failure. The standard leads (Fig. 13) showed a QRS conduction time of 0.10 second, a P-R interval of 0.20 second, pronounced left axis deviation, inversion of T_1 , and a bizarre QRS₂. The precordial lead showed T-wave inversion in the apical region, whereas QRS₄ was essentially normal.

The abnormal EV leads (Fig. 13, F. G.) showed an initial R wave of about 0.05 millivolt, followed by a notched S wave of 1.2 millivolts, an isoelectric RS-T segment, and a T wave of 0.1 millivolt. The EA lead showed an M-shaped QRS complex, followed by a diphasic T wave. Digitalis may have been responsible for part of the T-wave abnormalities. No known abnormalities indicative of coronary thrombosis were present in this case at any time; however, the QRS complex was abnormal in the EV leads. The position and size of the heart may have been responsible for the difference between QRS in the EV leads and QRS₄.

CASE 4 (*Questionable Coronary Occlusion*).—S. S., a retired business man, aged 55, gave an unreliable history which was similar to that of coronary occlusion; it began three years before admission, and continued as an "anginal syndrome" intermittently. On admission there were changes in the standard and precordial leads which suggested a toxic factor, such as digitalis, rather than primary myocardial disease. The patient denied having taken this drug. After ten days of rest in bed and withdrawal of all known cardiac medications, except as prescribed, the standard and precordial leads became essentially normal and resembled those taken elsewhere a few years earlier. After he had been digitalized with 15 grains of digifolin, the curves became abnormal and resembled those taken on admission. Therefore, it was felt that the patient was a malingerer. The patient was twice admitted elsewhere after discharge from our hospital. The opinions held were that the electrocardiograms were abnormal probably because of medication with digitalis-like drugs.

The EV leads (Fig. 13, S. S.), 52.5 and 55.0 cm. from the nares, showed no evidence of a Q wave. An R wave of 0.7 millivolt was the initial deflection and was followed by an S of 0.1 millivolt and a notched, upright T wave. The leads at 50 and 47 cm. showed an initial R wave of 0.2 millivolt, followed by a deep S wave of 3.0 millivolts and an upright T wave of 1.0 millivolt. These were normal for the EV lead within 5 cm. of the lower border of the auricle, as judged by the EA lead. The patient was in a semirecumbent position when the esophageal leads were taken.

The EA leads were obtained at the low level of 45.0 cm. and had elevated RS-T segments, with upright or diphasic T waves, presumably because of a toxic factor. The effect of digitalis on the EV lead was somewhat uncertain, for the T wave remained upright at all levels. In summary, no evidence of localized myocardial infarction was obtained by the routine, extremity, precordial, and esophageal leads in this case of what was probably malingering.

G. Other Factors Which Simultaneously Influence the Direction of the T Wave of the Esophageal Ventricular Leads and Precordial Ventricular Leads

Greater skepticism has arisen over inverted T waves than over the Q waves in the diagnosis of myocardial disease. A unimural left ventricular appearance of inverted T waves might be suggestive of a localized lesion. Adults normally have positive T waves in the apical and posterior ventricular leads. In the following cases, inversion of the T wave in leads from the apical and posterior ventricular regions occurred in the absence of QRS abnormalities in these leads. There was no conclusive history or objective indication of old or recent coronary occlusion in these cases.

CASE 1 (*Hypertensive Heart Disease With Left Ventricular Enlargement and Left Axis Deviation*).—S. L., a man, aged 36, probably had Cushing's syndrome. Chronic glomerulonephritis, multiple furunculosis, and hypertensive heart disease with a blood pressure ranging from 186/120 to 240/160 were known to have been present for one year. He had an elongated type of heart, with "25 per cent enlargement of the ventricles," and staphylococcus bacteremia. There was no history of coronary occlusion, and digitalis had not been given.

The standard leads (Fig. 14, S. L.) showed high voltage of the QRS deflections, left axis deviation, and a poorly defined, low, and diphasic T_1 , T_2 , and T_3 . Lead IV showed a normal QRS, and abnormal, minus-plus, diphasic, low voltage T waves. The EV lead showed a normal QRS, and an abnormal, inverted T of 0.2 millivolt. The EA potentials were normal. In summary, T-wave inversion was significant in leads from the left ventricle in this case.

CASE 2 (*Hypertensive Heart Disease With Left Ventricular Enlargement and a Normal Electrical Axis*).—S. E., a man, aged 46, complained of dyspnea on exertion, a localized precordial pain, and nocturia following an upper respiratory infection. No significant improvement had occurred during the preceding three years, during which time his blood pressure ranged from 170/90 to 210/110. The pulse rate averaged 80 beats per minute, the aortic second sound was accentuated, and there were no murmurs. Roentgenologic examination showed moderate enlargement of the left and right ventricles and a widened aortic arch. Urinalysis was negative. There was nothing to suggest that coronary occlusion had occurred, and the patient had not had congestive heart failure or taken digitalis.

The abnormalities in the standard leads (Fig. 14, S. E.) were confined to the diphasic T_1 and moderately inverted T_2 and T_3 . Lead IV and Lead EV were essentially the same, with small Q waves of 0.3 to 0.4 millivolt, R waves of 2.0 millivolts, and moderate inversion of the T waves. An S wave was present in Lead IV but not in the EV leads. The slightly depressed RS-T segments and moderately inverted T waves were found bimurally over the left ventricle. The EA potentials were not abnormal.

CASE 3 (*Left Bundle Branch Block in Arteriosclerotic Heart Disease*).—A. G., a man, aged 69, was hospitalized for six weeks because of an acute complaint suggesting coronary occlusion on the day of admission. The blood pressure was not abnormal. The left ventricle was slightly enlarged fluoroscopically; no murmurs were present.

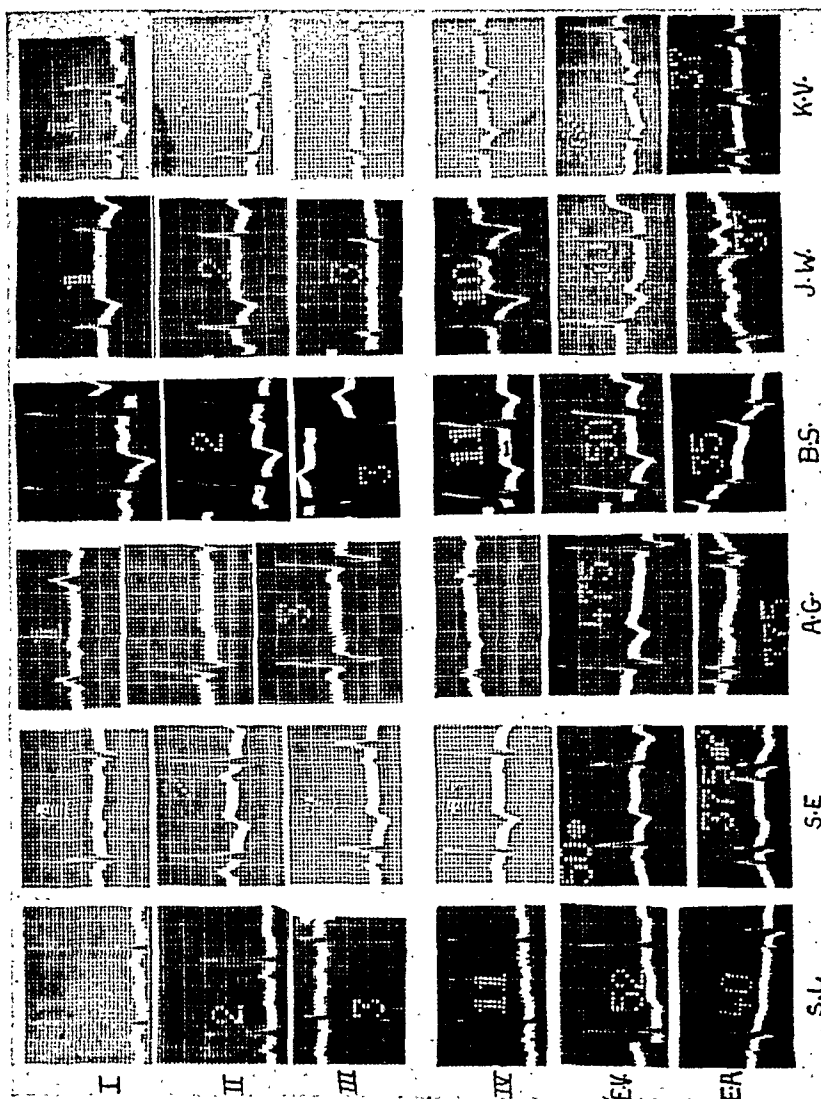


Fig. 14.—Factors which produce a bimodal inversion of T waves, as detected by the EV lead and Lead IV in six different cases.

The standard leads (Fig. 14, A. G.) showed left bundle branch block, with a QRS interval of 0.12 second. Lead IV showed a low, notched R wave of 0.5 millivolt and an inverted T wave in the V_5 - V_6 region. Lead EV showed a tall, notched R of 3.0 millivolts, with an inverted T of 0.5 millivolt. Lead EA showed diphasic T waves. No abnormal Q waves were present in Lead IV or Lead EV.

CASE 4 (*Left Axis Deviation and Left Ventricular Hypertrophy, With Aortic Stenosis*).—B. S., a man, aged 42, had been admitted several times because of a severe anginal syndrome, associated with rheumatic aortic stenosis, which developed late in life. Marked left ventricular hypertrophy was found fluoroscopically, and there was a palpable thrill over the aortic area. The pulse pressure was low, and the systolic level was consistent with the diagnosis. Six months before death the patient had a hemiplegia, but no evidence of myocardial infarction developed clinically. No autopsy was obtained.

The standard leads (Fig. 14, B. S.) showed high voltage of the QRS deflections, moderate left axis deviation, a QRS interval of 0.10 second, and inverted T_1 and T_2 . Leads IV and EV were very similar; both had R waves of about 3.0 millivolts, followed by small S waves and inverted T waves. Lead EA showed a diphasic T wave. In summary, T-wave inversion was again common to Lead IV and Lead EV over the left ventricle.

CASE 5 (*Toxic Factors, Including Digitalis*).—J. W., a woman, aged 63, had a positive blood Wassermann reaction, mitral stenosis, an enlarged heart, and auricular fibrillation with supraventricular tachycardia before she was first digitalized. She was later given Lugol's solution because of hyperthyroidism. There was no history of coronary occlusion.

The standard lead electrocardiogram (Fig. 14, J. W.) showed normal voltage of QRS and a normal electrical axis; T_1 and T_2 were abnormally inverted, presumably because of multiple factors. Chronic auricular fibrillation was also present; the ventricular rate had slowed before this special study.

The QRS groups in Lead IV and Lead EV were within normal limits. Inverted T waves were present anteriorly and posteriorly on the left (V_4 - V_6 region), and at all levels in the EV leads (Fig. 13, J. W.). The EA lead showed a normal QRS group and a positive T wave. Although the etiology of the alteration in the T waves was doubtful, there was no reason for ascribing inversion of T_4 and of T in Lead EV to coronary occlusion in this case.

CASE 6 (*Effects of Nutritional Deficiency, Superimposed on Probable Arteriosclerotic Heart Disease*).—K. V., a woman, aged 74, was admitted in a semicomatose state and remained psychotic for about six weeks, whereupon, with the administration of large doses of vitamin B, the psychosis disappeared within three days' time. Coronary occlusion was suspected initially, but conclusive indications of infarction never developed in the four routine leads. The rapid pulse rate slowed; the transverse diameter of the markedly enlarged heart decreased about 3 cm.; the pulmonary congestion cleared up; the peripheral edema over the arms, legs, and back disappeared; and the enlarged liver shrank until it was no longer palpable. Meanwhile, the blood pressure fluctuated from normal to high, and the loud, apical, mitral systolic murmur remained unchanged by the vitamin B therapy. The left ventricle was moderately enlarged, and the heart was of the elongated type as shown by fluoroscopic examination.

The standard lead electrocardiogram (Fig. 14, K. V.) showed normal conduction, slight left axis deviation, moderate inversion of T_1 and T_2 , and deep inversion of T_4 . Four weeks after admission, T_3 became slightly inverted. With the administration of vitamins B_1 and B_2 , T_1 and T_2 became less inverted, and T_3 became upright again. Lead IV and lead EV showed normal QRS groups; however, inverted T waves were present in the V_4 - V_6 region and in esophageal leads from the left ventricular region. The EA leads showed normal QRS and isoelectric T waves. Thus, it appears that, when myocardial disease involves an enlarged left ventricle, it is not unusual to observe inverted T waves anteriorly and posteriorly.

DISCUSSION AND CORRELATION

The exploratory leads used in this study were essentially unipolar with respect to a central, indifferent terminal. The changes of potential represented by the normal precordial leads were indicated by Lead IV in D. B., E. G., D. K. (Fig. 1), and R. W. (Fig. 2). These curves were similar to each other in most respects, and also very similar to normal

posterior ventricular leads (EV) in these same cases. Therefore, one may conclude that indirect exploratory leads from the normal anterior or posterior walls were similar in outline^{9, 10} with respect to the P wave, QRS, and T waves, regardless of whether the chest or the retrocardiac tissue separated the electrode from the normal left ventricle.

The indirect EA leads from the normal left auricle in these same cases (D. B., E. G., D. K., R. W.) showed diphasic P waves, with auricular intrinsic waves which identified the auricular level. In general, the characteristic QRST deflections appeared to be inverted images of those in exploratory leads from the left ventricle (EV and IV). The QRST waves in the EA leads also closely resembled those recorded by Wilson and his associates directly from the left ventricular cavity in experimental animals. Thus, in normal EA leads, the blood pool of the heart appeared to be the physical medium and the most direct path of conduction of the action currents produced by the ventricle. It is also responsible for conducting these currents away from the ventricular cavity to the auricular surface during the ventricular electrical cycle; this accounts for the typical form of the QRST complex (in the EA lead), which is the inverted image of the electrocardiogram obtained from the normal surface of the left ventricle. Other exploratory electrocardiograms on normal subjects, taken above the base of the heart, e.g., an esophageal lead opposite the aortic arch, or a unipolar lead of the right arm¹⁶ (using Wilson's central terminal as the indifferent electrode), are similar in form to the QRST complex in the EA lead. When apparently marked and gross abnormalities occur in myocardial infarction (cases B. C. and E. E., Fig. 2), the EA electrocardiogram and other exploratory electrocardiograms (not included in this paper) above the base of the ventricle are greatly altered from the normal potential found in these regions.

A deep Q wave occurred as the sole QRS complex in EV leads in three cases of posterior coronary occlusion, namely J. H. (Fig. 3), H. A. (Fig. 6), and N. K. (Fig. 10); these leads closely resembled precordial Lead IV in the case of anterior occlusion, B. C. (Fig. 2), and the EA lead of normal subject D. K. (Fig. 1). It appears that the common factor which produced similar QRS outlines⁹ was the large, inert mass of dead muscle in the infarct cases and the large pool of blood which electrically connected and effectively short-circuited the auricle and ventricle to the EA lead of the normal subject. Thus, both conduction paths, although they were technically different, actually permitted a recording of the action current variations from the ventricular cavity.

EV leads from the posterior myocardial infarct regions in which Q was not the sole QRS complex were obtained in seven cases, namely, E. E. (Fig. 2), L. B. (Fig. 4), C. L. (Fig. 5), L. D. (Fig. 7), F. N. (Fig. 8), O. S. (Fig. 9), and H. R. (Fig. 11). These deflections resembled the QRS group in EA leads from normal subjects D. B. (Fig. 1),

E. G. (Fig. 1), and R. W. (Fig. 2), and also the exploratory leads from the margins of experimental infarcts obtained by Wilson and his associates. Thus, it appeared that the EV leads in these cases were probably taken over areas in which the infarction did not involve all of the muscle under the electrode, rather than over the center of areas of complete infarction. These observations were, nevertheless, helpful in locating the lesion in the acute, subacute, and chronic stages of myocardial infarction, ranging from one day to sixteen years after the onset of the disease.

Significant RS-T segment elevation in EV leads occurred in only two cases of acute posterior infarction, namely, E. E. (Fig. 2) and L. B. (Fig. 4). Significant RS-T deviations in EV leads were not noted in the subacute or chronic stages of posterior myocardial infarction. A slight RS-T (Lead EV) segment depression occurred in the case of anterior occlusion, B. C. (Fig. 2). Wood and Wolferth⁶ and Wilson, et al.,^{3, 12} have shown that RS-T segment (Fig. 2) deviations disappear in a few hours from exploratory leads taken directly over cardiac infarcts produced in animal experiments. They also showed that, in direct leads from the side of the heart opposite the injured region, the RS-T displacement was electronegative, and, from the same side as the injury, electropositive. This is confirmed by the above observation in the EV lead for the RS-T segment is depressed (electronegative) in acute anterior myocardial infarction (B. C., Fig. 2) and elevated (electropositive) in acute posterior myocardial infarction (E. E., Fig. 2). In regard to T waves in the EV leads in cases of posterior occlusion, variable results were observed. In all of five cases of recent posterior occlusion, namely, E. E. (Fig. 2), J. H. (Fig. 3), L. B. (Fig. 4), G. L. (Fig. 5), and H. A. (Fig. 6), the T waves in EV leads were inverted. In three of five cases of old or healed lesions, namely, F. N. (Fig. 8), O. S. (Fig. 9), and H. R. (Fig. 11), the T waves were also inverted or diphasic; however, in two cases, namely, L. D. (Fig. 7) and N. K. (Fig. 10), the T waves were upright. The T wave remained electropositive in the case of anterior occlusion, B. C. (Fig. 2). Therefore, in general one may conclude, with regard to the QRST deflections in EV leads in cases of posterior myocardial infarction, that the deep Q wave, if present and abnormal, tends to persist for years, whereas the T waves, if inverted and abnormal, may remain inverted, or may become diphasic and upright during the process of healing. The RS-T segment elevation is transient, and it is significant only in some cases of acute posterior infarction. These deviations, if found together in the EV lead, are as specific indications of posterior myocardial infarction as similar deviations in Lead IV are of anterior myocardial infarction.¹³

Less specific signs of posterior myocardial infarction in EV leads, such as inversion of T while QRS and QRST remain essentially normal,

might occur with equal frequency in other types of myocardial disease, or in cases in which the infarct is small; however, if these changes suggest a localized myocardial lesion, they may be an aid in reaching a correct interpretation¹⁴ of the observed variations.

Some of the factors which were found to modify or produce abnormal QRS waves in EV leads were having the patient upright while recording, marked enlargement of the left auricle (not described in this paper), left axis deviation (Fig. 13, H. H.), intraventricular block with a short P-R interval (Fig. 13, T. B.), and marked left ventricular hypertrophy (Fig. 13, F. G.). Some of the factors which were found to modify, and tended simultaneously to invert, the T waves of the EV lead and Lead IV (V_4 - V_6) were extensive infarction, probably involving the posterior and lateral walls (Fig. 4, L. B., and Fig. 6, H. A.), multiple infarctions (not described in this paper), left ventricular enlargement caused by various diseases, such as hypertension (Fig. 14, S. L. and S. E.), left bundle branch block (Fig. 14, A. G.), aortic stenosis (Fig. 14, B. S.) and toxic or nutritional diseases of the myocardium (Fig. 14, J. W. and K. V.).

Our ability to differentiate myocardial lesions accurately is increased by the use of multiple precordial and multiple esophageal leads in conjunction with the standard leads, together with a knowledge of the clinical phenomena in a given case. Until the technique is much improved, roentgenkymography will be of little value in confirming a diagnosis of posterior myocardial infarction in the subacute or chronic stage of the disease.

The EV lead is of greatest value in interpreting doubtful changes in QRS_3 , and occasionally in QRS_2 , as illustrated in L. B. (Fig. 4, Feb. 23, 1940), F. N. (Fig. 8, 1934, 1936, and 1939), O. S. (Fig. 9, Dec. 8, 1939), N. K. (Fig. 10, 1935, 1939), and H. R. (Fig. 12, 1933, and Fig. 11, 1938). In each of these instances positive information concerning the presence of posterior myocardial disease was obtained by the EV lead.

The greatest value of the EA lead is in the study of auricular arrhythmias, as shown by Brown,⁸ in 1936, and more recently by Nyboer and Hamilton.¹⁵ The presence or absence of auricular intrinsic deflections in the P waves of juxta-auricular leads from the esophagus has been a valuable index of the anatomic relation of the electrode to the posterior part of the heart, and has made it possible to ascertain with greater accuracy the potentials of ventricular levels in normal subjects and patients with heart disease. Although the QRST complexes from the esophageal auricular leads in normal subjects have fixed patterns, the interpretation of abnormalities in these leads is still very difficult. In the cases reported herein, the T wave in EA leads was inverted, diphasic, upright, or nearly isoelectric in various forms of myocardial disease; however, the normal T waves in EA leads were inverted (Fig.

1). At present, the cause and significance of the major changes in the form of the QRST complexes of the esophageal auricular electrocardiograms are not fully understood.

SUMMARY

1. The standard leads, a selected precordial lead (IV), and selected esophageal leads from the ventricular (EV) and auricular (EA) levels were taken on four normal subjects, in one case of anterior infarction, and in ten cases of posterior myocardial infarction.

2. Similar studies were made on ten other patients who had a history, physical signs, or something else to suggest myocardial disease, in order to differentiate the abnormalities which they presented from the more specific electrocardiographic indications of coronary occlusion.

3. Study of two typical cases of posterior myocardial infarction by means of the roentgenkymograph yielded no information.

4. The esophageal ventricular electrocardiograms which were characteristic of posterior myocardial infarction closely resembled precordial electrocardiograms which were characteristic of anterior myocardial infarction, and vice versa.

5. In some cases in which the standard lead electrocardiograms were equivocal, a definite diagnosis of posterior myocardial infarction was made by means of the esophageal juxtaventricular leads.

6. The ventricular complex of the esophageal juxta-auricular electrocardiogram was often found to be altered in cases of myocardial disease.

CONCLUSION

Our knowledge of the complex electrical field of the heart will never be complete until the diseases of the human myocardium are studied by indirect electrical explorations of the posterior, lateral, and anterior walls of the ventricles and of the right and left auricles, as well as by the standard lead electrocardiogram. Specific and helpful knowledge regarding the form of the electrocardiogram opposite the ventricle posteriorly was obtained with an esophageal lead in many cases of posterior myocardial infarction, whether acute or chronic.

I wish to express my appreciation to Dr. Robert H. Halsey, Dr. Charles A. Poindexter, and Dr. Charles E. Kossmann for their helpful criticism in the preparation of this paper and to Marcella F. Hughes, Beatrice Tanney, and Alice Hughes for their personal assistance in this problem.

REFERENCES

1. Wilson, Frank N., Wishart, Shelby W., and Herrmann, George R.: Factors Influencing Distribution of Potential Differences Produced by Heart Beat at Surface of Body, *Proc. Soc. Exper. Biol. & Med.* 23: 276, 1926.
2. Wilson, Frank N., Barker, Paul S., MacLeod, A. Garrard, and Klostermyer, L. L.: The Electrocardiogram in Coronary Thrombosis, *Proc. Soc. Exper. Biol. & Med.* 29: 1006, 1932.

3. Wilson, Frank N., Hill, Ian G. W., and Johnston, Franklin D.: The Form of the Electrocardiogram in Experimental Myocardial Infarction.
 I. Septal Infarcts and the Origin of the Preliminary Deflections of the Canine Levocardiogram, *AM. HEART J.* 9: 596, 1934.
 II. The Early Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, *AM. HEART J.* 10: 889, 1935.
 III. The Later Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, *AM. HEART J.* 10: 903, 1935.
 IV. Additional Observations on the Later Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, *AM. HEART J.* 10: 1025, 1935.
4. Wolferth, Charles C., and Wood, Francis Clark: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am. J. M. Sc.* 183: 30, 1932.
5. Wood, Francis Clark, Bellet, Samuel, McMillan, Thomas M., and Wolferth, Charles C.: Electrocardiographic Study of Coronary Occlusion. Further Observations on the Use of Chest Leads, *Arch. Int. Med.* 52: 752, 1933.
6. Wood, Francis Clark, and Wolferth, Charles C.: Experimental Coronary Occlusion. Inadequacy of the Three Conventional Leads for Recording Characteristic Action Current Changes in Certain Sections of the Myocardium; an Electrocardiographic Study, *Arch. Int. Med.* 51: 771, 1933.
7. Lieberman, Abraham, and Liberson, Frank: An Internal Electrocardiographic Lead, *Proc. Soc. Exper. Biol. & Med.* 31: 441, 1934.
8. Brown, W. Hurst: A Study of the Esophageal Lead in Clinical Electrocardiography, *AM. HEART J.* 12: 1, 307, 1936.
9. Hamilton, James G. M., and Nyboer, Jan: The Ventricular Deflections in Myocardial Infarction—An Electrocardiographic Study Using Esophageal and Precordial Leads, *AM. HEART J.* 15: 414, 1938.
10. Nyboer, J.: The Esophageal Electrocardiogram in Coronary Thrombosis, *J. Clin. Investigation* 18: 495, 1939.
11. Gubner, Richard, and Crawford, J. Hamilton: Roentgenkymographic Studies of Myocardial Infarction, *AM. HEART J.* 18: 8, 1939.
12. Wilson, Frank N., Hill, Ian G. W., and Johnston, Franklin D.: The Interpretation of the Galvanometric Curves Obtained When One Electrode Is Distant From the Heart and the Other Near or in Contact With the Ventricular Surface. I. Observations on the Cold Blooded Heart, *AM. HEART J.* 10: 163, 1934.
13. Kossman, Charles E., and de la Chapelle, Clarence E.: The Precordial Electrocardiogram in Myocardial Infarction. I. Observations on Cases With Infarction Principally of the Anterior Wall of the Left Ventricle and Adjacent Septum, *AM. HEART J.* 15: 700, 1938.
14. Wilson, Frank N.: The Electrocardiogram in Diseases of the Coronary Arteries, Chapter XII in Levy, Robert L. (ed.): *Diseases of the Coronary Arteries and Cardiac Pain*, New York, 1936, The Macmillan Co.
15. Nyboer, Jan, and Hamilton, James G. M.: Oesophageal Electrocardiograms in Auricular Fibrillation, *Brit. Heart J.* 2: 263, 1940.
16. Kossmann, Charles E., and Johnston, Franklin D.: The Precordial Electrocardiogram. I. The Potential Variations of the Precordium and of the Extremities in Normal Subjects, *AM. HEART J.* 10: 925, 1935.

OBJECTIVE EVIDENCE OF THE EFFICACY OF MEDICINAL THERAPY IN ANGINA PECTORIS

A. STONE FREEDBERG, M.D., JOSEPH E. F. RISEMAN, M.D., AND
ERWIN D. SPIEGL, M.D.
BOSTON, MASS.

IN THE treatment of patients with angina pectoris some form of medication is usually prescribed, but in the selection of such drugs the physician must rely either on clinical impressions of their therapeutic value or on the unsupported claims of the manufacturers. Many attempts to prove the value of medication have been made, but there has been little objective evidence of therapeutic action. As a result, the Council of Pharmacy and Chemistry of the American Medical Association, in 1937,¹ in reviewing the claims for the therapeutic efficacy of xanthine derivatives, reversed their decision of 1930,² and "decided that there is no warrant for claims of efficacy as a dilator of the coronary arteries or of usefulness in overcoming pain in coronary occlusion or angina pectoris." The purpose of the present investigation is to review the literature and present objective evidence of the pharmacodynamic action of drugs under conditions comparable to those commonly used in the treatment of angina pectoris.

REVIEW OF THE LITERATURE

Experiments on Laboratory Animals

Experiments on laboratory animals have been carried out to ascertain the effect of drugs on the coronary arterial blood flow (Table I). Such studies include measurements of the caliber of isolated arterial rings, and measurements of the coronary blood flow in isolated, perfused hearts, in heart-lung preparations, and in intact animals (as indicated by a stromuhr or by the venous return through the coronary sinus). Despite unavoidable differences in technique and differences in the animals used, the results are extraordinarily consistent and indicate that the nitrites and purines cause coronary vasodilatation and an increased coronary blood flow, and that digitalis usually has the opposite effect. There are definite objections to these studies, however, for the results obtained under artificial conditions in normal animals are

From the Medical Research Department of the Beth Israel Hospital and the Department of Medicine, Harvard University, Boston.

Presented before the American Society for Clinical Investigation, Atlantic City, N. J., May, 1940.

Received for publication Feb. 21, 1941.

not necessarily applicable to coronary artery disease in man; furthermore, it is difficult to ascertain whether the concentrations of the drugs used in these experiments were comparable to what might be present in the circulating blood of patients taking such drugs.

The effect of drugs on the collateral circulation has been studied after experimental occlusion of a main coronary artery, but conflicting results have been obtained (Table I). The pathologic anatomy and physiology of acute experimental coronary occlusion are not comparable, however, to those of angina pectoris as it is seen clinically. As Schlesinger, Blumgart, and their coworkers^{3, 4} have shown, an anastomotic circulation may not develop following *acute coronary occlusion*, whereas the hearts of the patients with angina pectoris possess a rich, functioning collateral circulation, presumably as a result of *chronic narrowing* of the main coronary arteries.

Studies on Patients With Angina Pectoris

Clinical Observations and Impressions.—The number of clinical reports which indicate that the purines are of value in the treatment of angina pectoris is too large to list; certain results and methods of study, however, deserve mention. Askanazy⁵ administered theobromine sodium salicylate to patients for three weeks, alternating with similar periods without medication. His results may be translated as follows: "With the certainty (Sicherheit) of an experiment the attacks disappeared at once, or very soon after the administration of theobromine, and recurred as soon as the drug was stopped." Gilbert and Kerr⁶ obtained similar results with theobromine sodium acetate in thirty-seven of sixty-nine patients; twenty showed no response to this drug. Smith, Rathe, and Paul,⁷ using theophylline, found "that in a fairly large percentage favorable results were shown . . . increases in dosage helped patients in whom the results of the medication had been in doubt."

Controlled Clinical Observations.—In 1933, Evans and Hoyle⁸ reported the results of two and one-half years of observation on ninety patients with angina who were given various types of medication alternating with a placebo, and who kept a careful record of their attacks. They found "that a measure of improvement appears to result from every remedy tried, and at least as great an improvement appears during treatment with placebo . . . we have been unable to convince ourselves that any drug tested is worthy of trial in the routine treatment of the disease." Master, et al.,^{9, 10} and Gold, Kwit, and Otto¹¹ corroborated these observations; the latter stated "that patients with cardiac pain are unable to distinguish the effects of a placebo from those of a xanthine when measures are taken to preclude the identification of the agent by any means other than the relief of pain. It is concluded that the xanthines exert no specific action which is useful in the routine

TABLE I
SUMMARY OF EXPERIMENTAL STUDIES ON THE EFFECT OF DRUGS ON THE CORONARY BLOOD FLOW

DRUGS USED	MEASUREMENT OF DIAMETER OF ISOLATED RINGS OF CORONARY ARTERIES IMMERSSED IN PHYSIOLOGIC SOLUTIONS TO WHICH DRUGS HAVE BEEN ADDED*			MEASUREMENT OF CORONARY BLOOD FLOW IN HEART-LUNG PREPARATIONS OR ISOLATED, PERFUSED HEARTS*			MEASUREMENT OF CORONARY BLOOD FLOW IN INTACT ANIMALS		
	CORONARY ARTERY DILATATION	CORONARY ARTERY CONSTRICTION	NO EFFECT	CORONARY FLOW		NO EFFECT	CORONARY FLOW		NO EFFECT
				INCREASED	DECREASED		INCREASED	DECREASED	
<i>Nitrites</i>									
Nitro-glycerin	Voegtlin et al. ³⁷			Katz et al. ^{50, 57} Smith et al. ⁵³			LeRoy ⁵³ Meyer ⁵⁵ Schloss ⁵⁷ Wégria ⁵⁸ Essex et al. ^{59, 60}	Bond ⁵⁶	
Amyl nitrite	Cow ²⁸ Loeper et al. ²⁹ Voegtlin et al. ³⁷ Pal ¹⁰			Loeb ⁵³ Bodo ⁶⁰ Krawkow ⁴⁷			Francois-Frank ⁶¹ Essex et al. ⁵⁹ Meyer ⁵⁵ Schloss ⁵⁷ Wégria ⁵⁸	Bond ⁵⁶	
Octyl nitrite	Krantz et al. ⁴¹			Krantz et al. ⁴¹			Krantz et al. ⁴¹		
Sodium nitrite	Voegtlin and Mach ³⁷ Loeper et al. ²⁹ Kountz, ⁴² Cow ²⁸ Eppinger and Hess ⁵³ Pal ¹⁰			Katz et al. ^{50, 57} Bodo, ⁶⁰ Kountz and Smith ⁶¹ Kountz, ⁴² Wedd ⁶² Fowler et al. ⁶³			Schloss ⁵⁷		
<i>Purines</i>									
Theobromine	Pal ¹⁰ Eppinger and Hess ⁵³		Voegtlin and Mach ³⁷	Loeb ⁵³ Heathcote ⁶¹ Kountz and Smith ⁶¹ LeRoy ⁵⁵ Krawkow ^{47, 66} Wolchansky ⁶⁷			Smith and Miller ⁶² LeRoy ⁵⁵ Gilbert and Fenn ⁵³	Bond ⁵⁶	
Theobromine sodium salt-cyclate				Smith et al. ⁵³ Kountz and Smith ⁶¹ Heathcote ⁶¹ Wolchansky ⁶⁷			Sakai and Saneyoshi ⁶⁴ Gilbert and Fenn ⁵³		
Theobromine sodium acetate				Fowler et al. ⁶³			Gilbert and Fenn ⁵³		

Theophyllin				Katz et al. ^{6d} Smith et al. ⁵⁸ Guggenheimer and Sassa ⁶³ Kountz and Smith ⁶¹ Fisher et al. ⁶² Heathcote ⁶¹					Smith and Miller ⁶² Gilbert and Fenn ⁶³																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														</
-------------	--	--	--	---	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	----

TABLE I—CONT'D

DRUGS USED	MEASUREMENT OF DIAMETER OF ISOLATED RINGS OF CORONARY ARTERIES IMMERSSED IN PHYSIOLOGIC SOLUTIONS TO WHICH DRUGS HAVE BEEN ADDED*				MEASUREMENT OF CORONARY BLOOD FLOW IN HEART-LUNG PREPARATIONS OR ISOLATED, PERFUSED HEARTS*				MEASUREMENT OF CORONARY BLOOD FLOW IN INTACT ANIMALS			
	CORONARY ARTERY DILATATION	CORONARY ARTERY CONSTRUCTION	NO EFFECT		CORONARY FLOW		NO EFFECT		CORONARY FLOW		NO EFFECT	
					INCREASED	DECREASED			INCREASED	DECREASED		
Miscellaneous (A)												
Sodium acetate					Guggenheimer and Sassa ⁶⁸				Gilbert and Fenn ⁷³			
Ethylene-diamine hydrochloride					Iwai and Sassa ⁷⁰							
Quinidine and quinine		Krawkow ¹⁷	Kountz ¹²		Hedborn ⁷⁵ Starr ⁷⁶	Bodo ⁶⁰	Bodo ⁶⁰ Kountz ¹² Rabe ⁷⁸					
Histamine ⁽¹⁾	Kountz ¹²	Barbour ¹⁸ Anrep ⁵⁰ Rothlin ⁵⁰ Kountz ¹² Cruickshank and Subba-Rau ¹⁶	Gunn ⁶³		Katz et al. ^{56, 57} Narayana ⁸⁰ Kountz and Smith ^{61, 6} Kountz ¹² Müller et al. ⁸¹	Kountz and Smith ^{61, 10} Krawkow ^{47, 60}			Gunn ⁶³ Rühl ⁹⁸ Sumbal ⁹⁹ Wégria et al. ⁸⁸ Shill ¹⁰² Gunn ⁶³	Dale and Laidlaw ¹⁰⁰ Viotto ¹⁰¹ Feldberg and Shill ¹⁰² Gunn ⁶³		
Acetylcholine		Wedd ⁶² Eppinger and Hess ⁵³ Lange ⁴⁵			Narayana ⁸⁰ Katz et al. ^{56, 57}	Wedd and Fenn ⁵¹ Katz et al. ⁵⁷	Narayana ⁸⁰		Sumbal ⁹⁹ Essex et al. ⁸⁹			
Tissue extracts ¹¹	Lange ⁴⁵				Lange ⁴⁵ Kountz and Smith ⁶¹ Fisher et al. ⁶⁹ Frey and Kraut ⁸³ Haberlandt ⁸⁴ Wedd ^{51, 62}				Essex et al. ⁸⁹			
Adrenalin	Cruickshank and SubbaRau ¹⁶ Cow, ⁸⁸ Kountz ¹² Eppinger and Hess ⁵³ Pal ¹⁰	Kountz ¹² Meyer ⁵²			Anrep and Stacy ⁷³ Krawkow ^{47, 60} LeRoy ⁶³ Katz et al. ^{60, 57} Kountz and Smith ^{61, 10}	Katz et al. ⁵⁷ Kountz and Smith ^{61, 6} Anitschkow ⁷¹			LeRoy ⁶³ Bond ⁸⁶ Essex et al. ⁸⁹ Wégria et al. ⁸⁸			
Posterior pituitary preparations	Cow, ⁸⁸ Kountz ¹²	Cow, ⁸⁸ Pal ^{10, 53, 54}				Bodo ⁶⁰ Kountz ¹² Anrep and Stacy ⁷³ Narayana ⁸⁰ Katz et al. ^{56, 57} Wedd ⁶²			Sumbal ⁹⁹	LeRoy ⁶³ Essex et al. ⁸⁹ Gunn ⁶³ Wégria et al. ⁸⁸		

TABLE I—CONT'D

TABLE 1—CONT'D

STUDIES OF EFFECT OF DRUGS ON COLLATERAL CORONARY CIRCULATION OF ANIMALS FOLLOWING ACUTE EXPERIMENTAL OCCLUSION OF MAIN CORONARY ARTERY										MISCELLANEOUS STUDIES	
DRUGS USED	SIZE OF INFARCT		INTENSITY OF CYANOSIS		ABILITY OF INVOLVED AREA TO CONTRACT		CORONARY BLOOD FLOW		ELECTROCARDIOGRAPHIC CHANGES	PREVENTION OF ELECTROCARDIOGRAPHIC CHANGES INDUCED BY ADRENALIN	
	SMALLER	NO CHANGE	DECREASED	NO CHANGE	RESTORED	NOT RESTORED	INCREASED	UNCHANGED	REVERSED		NOT REVERSED
Nitrites											
Nitro-glycerin			Smith ¹⁰⁸								Douglas et al. ¹⁰⁸
Amyl nitrite						Wiggers and Greene ¹⁰⁷					
Octyl nitrite						Wiggers and Greene ¹⁰⁷		Wiggers and Greene ¹⁰⁷			
Sodium nitrite											
Purines											
Theobromine											
Theobromine sodium salicylate											
Theobromine sodium acetate								Wiggers and Greene ¹⁰⁷			
Theophyllin								Wiggers and Greene ¹⁰⁷			
Theophyllin sodium acetate								Wiggers and Greene ¹⁰⁷			
Theophyllin ethylenediamine (E)	Fowler et al. ¹⁰⁹ Mahaim and Rothberger ¹⁰¹ Laubry et al. ¹⁰³	Gold et al. ¹⁰³	Fowler et al. ¹⁰⁹ Mahaim and Rothberger ¹⁰¹ Laubry et al. ¹⁰³			Wiggers and Greene ¹⁰⁷			Mahaim and Rothberger ¹⁰¹ Laubry et al. ¹⁰³	Gold et al. ¹⁰³	

A, In addition to the substances listed in the table, the following substances produced dilatation in heart-lung preparations or perfused heart preparations: Amphetamine sulfate (LeRoy),⁴³ camphor (Bodo),⁶⁰ (Kountz),⁴² pilocarpine (Kountz),⁴² papaverine (Kountz),⁴² hypertonic sodium chloride (Katz et al.),⁵⁶ hypertonic calcium chloride (Katz et al.),⁵⁶ increased acidity of perfusion fluid (Smith et al.),⁵³ lack of oxygen (Richards),¹⁰⁰ increase in carbon-dioxide content (Anrep),⁴⁶ atropine (Hedborn),⁵⁵ diffusion substances liberated in myocardial ischemia (Katz et al.).⁵⁰

The following substances produced constriction in the same type of preparation: Potassium chloride (Katz et al.),⁵⁰ atropine sulphate (Katz et al.),⁵⁶ (Kountz),⁴² insulin (Bodo),⁶⁰ nicotine (Kountz),⁴² (Krawkow),⁶¹ barium chloride (Anitschkow),⁷⁴ (Krawkow),⁶¹ pilocarpine (Krawkow).⁶⁰

In the intact unanesthetized animal the following substances produced an increase in coronary artery blood flow: Amphetamine sulphate (LeRoy),⁴³ papaverine (Essex et al.),⁸⁰ atropine sulphate (Essex et al.).⁸³

In the intact anesthetized animals the following substances produced an increase in coronary artery blood flow, 1, 3-dimethyl-8-ethyl-xanthine (LeRoy and Speer),¹¹⁰ and 1,3-diethyl-8-methyl-xanthine (LeRoy and Speer).¹¹⁰

*Studies of Kountz,⁴² Kountz and Smith,⁶¹ Anitschkow,⁷⁴ Krawkow,⁶¹ were carried out on human hearts shortly after death. The studies by other investigators were carried out on laboratory animals.

B, In the studies of Wedd,⁴² and Wedd and Fenn,⁸¹ adenosine, yeast, and muscle adenylic acid were used. The tissue extracts used by other investigators were of an unknown chemical nature.

G, Undilated human hearts were used in these studies.

D, Dilated human hearts were used in these studies.

E, In the experiments of Davis,⁷² a constant head of pressure was employed to produce uniform distention of the coronary arteries. Any variation in the flow, therefore, was interpreted as due to changes in the coronary capillary blood flow.

F, In the studies of Voegtlin and Macht,³⁷ digitalin, digitalin, digitoxin, tincture of digitalis and butagin caused coronary artery constriction. The water soluble digitonin and digalen produced dilatation. The infusion of digitalis caused constriction, followed by dilatation.

G, According to most investigators, the effect of histamine varies in different animal species. Thus in the intact cat, dog, and turtle, dilatation or an increased coronary blood flow is obtained, whereas, in the rabbit and guinea pig, constriction or a decreased coronary blood flow is induced.

treatment of cardiac pain." Massell,¹² using a similar technique for the relief of angina pectoris, found, however, that "the xanthines used, especially theocaine, offer a better chance for the relief of angina pectoris in the ratio of 2 to 1 than aspirin, sodium bicarbonate, phenobarbital, or a combination of the latter two."

Objective Studies on Patients With Angina Pectoris.—Riseman and Brown,^{13, 14} in a similar study, concluded: "it is obviously impossible to estimate how much of the apparent improvement was due to medication." They therefore measured the amount of work which patients could do following the administration of drugs and placebos. They found that "patients whose treatment consisted of lactose, sodium bicarbonate, potassium iodide, or tissue extract were unable to perform any more work than was possible without medication. . . ," whereas "one-half of the patients were benefited by using aminophyllin or quinidine sulfate." The value of nitroglycerin, erythrol tetranitrate, and atropine sulfate was demonstrated in a similar fashion. Wayne and Laplace,¹⁵ using a similar method, obtained similar results with nitroglycerin, erythrol tetranitrate, and aminophyllin intravenously. Missal¹⁶ and Kisch¹⁷ also found that nitroglycerin and xanthine derivatives increased the exercise tolerance of patients with angina pectoris. Proger, Minnich, and Magendantz¹⁸ found that "the abolition of cardiac irregularities by the use of quinidine sulfate resulted in a striking increase in the capacity for work without pain."

In 1932, Goldhammer and Scherf¹⁹ showed that electrocardiograms taken during attacks of angina induced by deep knee bending revealed changes in the S-T segment and the T wave. These changes could be prevented and the amount of work performed could be increased by the administration of atropine sulfate before the onset of work. Larsen,²⁰ in 1938, found that the administration of nitroglycerin did not prevent the electrocardiographic changes which were induced by anoxia in patients with angina pectoris. Raab and Schönbrunner,²¹ in 1939, found that the electrocardiograms of ten of fifteen patients with "an electrocardiogram of hypoxia" at rest or during exercise showed a tendency to become normal after roentgen irradiation of the adrenals. Levy, Bruenn, and Williams,^{22, 23} in 1939, found that the administration of aminophyllin and nitroglycerin before breathing an atmosphere containing 10 per cent oxygen prolonged the time necessary to induce pain, and resulted in less change in the RS-T segments than was observed following lactose or no medication. When given intravenously, aminophyllin was more effective than nitroglycerin.

A survey of the literature on electrocardiographic changes during attacks of angina pectoris shows a marked difference of opinion as to the frequency and character of such changes.²⁴ This is probably due to differences in technique and different time relationships between the occurrence of pain and the recording of the electrocardiogram. Rise-

man, Waller, and Brown,²⁴ who took electrocardiograms *continuously* during exercise and during anoxia, have shown that the most constant change is a deviation (usually a depression) of the S-T segment in the precordial lead; this occurs before the onset of pain and disappears shortly after cessation of pain. Changes in the T wave were more common during recovery than during the attack. These investigators also found that the electrocardiographic changes induced by exertion could be prevented by the inhalation of pure oxygen before and during the exercise.

METHODS OF STUDY

Fifteen patients (fourteen men and one woman) with angina pectoris were studied. The youngest patient was 39 years of age; twelve were more than 50; the oldest was 56. The patients had been observed in a special clinic at weekly intervals for periods of one and one-half to seven years. At each visit the number of attacks experienced during the previous week was reported, and the amount of work necessary to induce pain was measured under standardized conditions.²⁵ All tests were carried out in a room maintained at a temperature of 45 to 55° F., approximately one hour after a light breakfast, and following at least one-half hour of rest after coming to the clinic; no tests were made if pain had been experienced on the way to the hospital; only one test was performed on any day. The exercise consisted of repeatedly mounting and descending a two-step staircase under the above conditions until the onset of pain.

On several visits electrodes were attached to both arms below the insertion of the deltoid muscles and also to the precordium over the cardiac apex. A precordial lead (IV R) was taken with the patient standing at rest; the exercise test was then repeated under the same standardized conditions, with the electrodes in place and the electrocardiographic machine (but not the camera) running continuously. Immediately before the cessation of exercise the camera was started, and a tracing was obtained for at least fifteen seconds after the onset of the attack; additional tracings were taken at one-minute intervals for five minutes after the cessation of pain.

After these studies were completed, drugs were administered in the usual therapeutic doses, and after an appropriate interval the exercise and electrocardiographic studies were repeated on at least two different days in an identical fashion.

The tests with nitroglycerin were carried out two minutes after the administration of a single dose (0.3 mg.). No other medication was administered for one week prior to these tests.

In the studies of theobromine sodium acetate, enteric-coated tablets (0.5 Gm.) were administered four times daily (on arising, after lunch, after supper, and before retiring) for one week; on arriving at the laboratory an additional dose (0.5 Gm.) of uncoated theobromine sodium acetate was administered. One to two hours later the electrocardiogram during exercise was obtained in the usual manner. Enteric-coated tablets of lactose, which were identical in appearance with the purine tablets, were used for control experiments; these were administered in the same manner and the tests carried out in an identical fashion.

The tests with quinidine sulfate were carried out after administering 0.3 Gm. of the drug four times daily for one week, with an additional dose one to two hours before the exercise and electrocardiographic tests. The inert substance used as a control for these studies was tablets of sodium bicarbonate (0.3 Gm.), which resembled the quinidine in appearance.

Studies on digitalis were performed in a somewhat different manner. Electrocardiograms were taken according to the technique described above, except that one precordial (IV R) and three standard leads were taken *continuously* before, during,

and after the exercise on four different days, during which period the patient received no medication. Tablets of digitalis leaf were then administered; 0.1 Gm. (1 cat unit) was given four times the first day and three times daily thereafter in an attempt to administer a full digitalizing dose according to the weight method of Eggleston.²⁶ All three patients, however, discontinued the medication, because of marked increase of pain, before receiving this calculated dose. The three patients weighed 140, 165, and 170 pounds, and received 1.4 Gm., 1.4 Gm., and 1.6 Gm., respectively, in a period of five days. Each patient returned to the clinic daily, at which time he reported the number of attacks he had experienced, and a four-lead electrocardiogram was obtained with the patient standing at rest. Exercise tests, using Lead IV R, were performed, in the manner described above, on two patients after the maximum degree of digitalization had been obtained, and, in the third subject, four days after digitalis was discontinued.

In the study of the electrocardiographic changes, ten consecutive complexes were measured and averaged. The terminal portion of the P-R interval was taken as the isoelectric level.

RESULTS

The amount of exercise necessary to produce pain was relatively constant (within six trips) for each of the fifteen patients. Immediately after the onset of pain caused by exercise, the electrocardiograms of all but one subject showed a depression of the S-T segment of 1 to 4 mm., as compared with the tracing taken at rest; the degree of depression was constant for each patient. The results after the administration of lactose or sodium bicarbonate were identical with those obtained when no medication was given. There was no correlation between the degree of depression of the S-T segment and the amount of work necessary to produce pain. Changes in the P, QRS, and T waves were inconstant and of little importance in these studies. There was nothing significant about the electrocardiogram during recovery from exercise and pain, except after the administration of digitalis.

The patients could be divided into three groups, according to their response to medication. The patients in Group I, after medication, showed little or no depression of the S-T segment as a result of exercise, and were able to do over 50 per cent more work than was possible when they were not taking drugs. Those in Group II, after medication, showed less depression of the S-T segment after exercise, and were able to do more work than was previously possible; these patients, however, showed some depression of the S-T segment after exercise, and developed pain when they performed 50 per cent more work than was possible when they were not taking drugs. The patients in Group III were not benefited by medication; after exercise they showed essentially the same changes in the S-T segment and were able to do no more work than was possible without medication. In general, when no medication was taken, the patients in Group I showed less depression of the S-T segment after exercise than did those in Group II or III.

Results With Nitroglycerin

The effect of nitroglycerin was studied on thirteen patients (Table II). Nine patients showed a marked response (Group I) (Fig. 1). In this

TABLE II

OBJECTIVE EVIDENCE OF THE EFFICACY OF NITROGLYCERIN IN PATIENTS WITH ANGINA PECTORIS

PA- TIENT	NO MEDICA- TION†		2 MINUTES AFTER NITROGLYCERIN $\frac{1}{200}$ GRAIN							
			NO INCREASE* IN WORK		50% IN- CREASE* IN WORK		100% IN- CREASE* IN WORK		MORE THAN 100%* IN- CREASE IN WORK	
	NO. OF TRIPS	S-T SEG- MENT DEPRES- SION (MM.)	NO. OF TRIPS	S-T SEG- MENT DEPRES- SION (MM.)	NO. OF TRIPS	S-T SEG- MENT DEPRES- SION (MM.)	NO. OF TRIPS	S-T SEG- MENT DEPRES- SION (MM.)	NO. OF TRIPS	S-T SEG- MENT DEPRES- SION (MM.)
<i>Group I. S-T Changes Diminished Markedly Following Medication</i>										
M. B.	36	3.0	36†	0.2			54†	0.5	72	1.5
S. E.	27	2.7	27†	0.2			100†	1.2	190†	1.5
S. R.	51	2.7	51†	0.5	75†	1.0				
H. Shl.	54	2.5	54†	0.4	75†	0.4				
B. L.	18	2.3	18†	0.5	26†	0.5				
M. L.	40	1.8	40†	0.0	64†	0.5				
H. Shr.	22	1.5	22†	0.0	36†	0.5	50†	0.3	100†	1.5
S. L.	26	1.5	26†	0.0	42†	0.2	60†	1.5		
R. C.	26	1.0	26†	0.0	39†	0.0				
<i>Group II. S-T Changes Diminished Moderately Following Medication</i>										
P. R.	49	3.5	49†	1.9	62	2.0				
L. W.	36	2.7	36†	2.5	61	1.0				
<i>Group III. S-T Changes Not Prevented by Medication</i>										
S. W.	38	1.6	38†	1.6	50†	1.6				
B. A.	50	4.0	50	3.0						

*Increase in work as compared with the amount necessary to induce pain when no medication was given.

†No attack of angina was induced.

‡Exercise was continued until attack was produced.

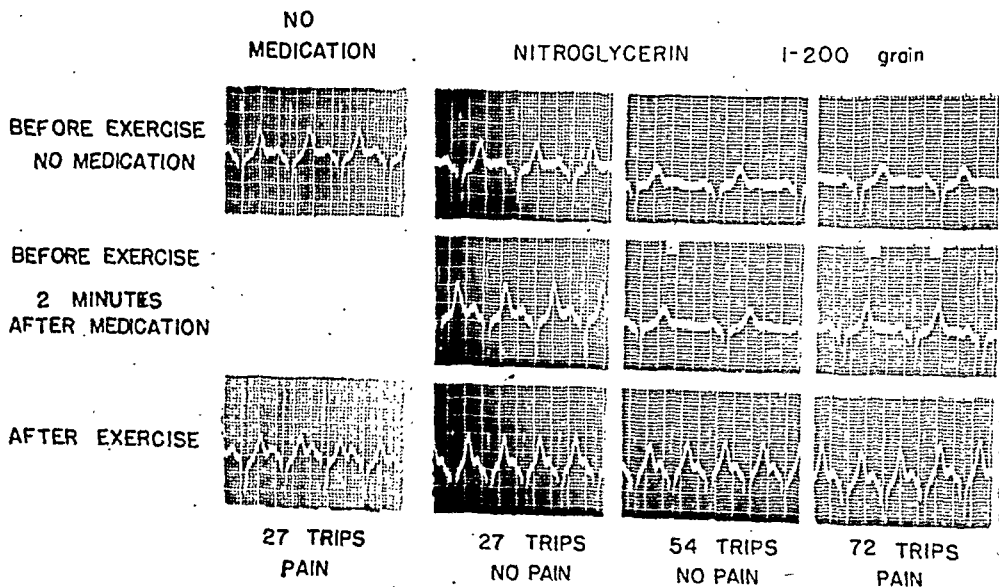


Fig. 1.—Marked response to nitroglycerin (Group I), as illustrated by results on Patient S. E. When no medication was administered, twenty-seven trips over the two-step staircase caused pain and a depression of the S-T segment averaging 2.7 mm. Two minutes after the sublingual administration of nitroglycerin, the same amount of work caused no pain and almost no change in the level of the initial portion (take-off) of the S-T segment; 100 per cent more work caused no pain and an average S-T depression of 0.5 mm; 150 per cent increase in work caused pain and an average S-T depression of 1.5 mm.

group the average depression of the S-T segment without medication was 2.1 mm. After the administration of nitroglycerin (0.3 mg.), the amount of work which previously induced pain caused an average depression of the S-T segment of only 0.2 mm., and no pain was experienced.

Two patients showed a moderate response to nitroglycerin (Group II). When no medication was taken, exercise sufficient to induce pain caused an average S-T depression of 3.1 mm. After medication, both patients performed 50 per cent more work before developing pain; the average depression of the S-T segment after this increased amount of work was 2.2 mm.

The remaining two patients showed no response (Group III); after exercise, approximately the same depression of the S-T segment occurred, both with and without medication. One was not benefited in any way by the drug (Fig. 2); the other was able to do more work than when nitroglycerin was not taken.

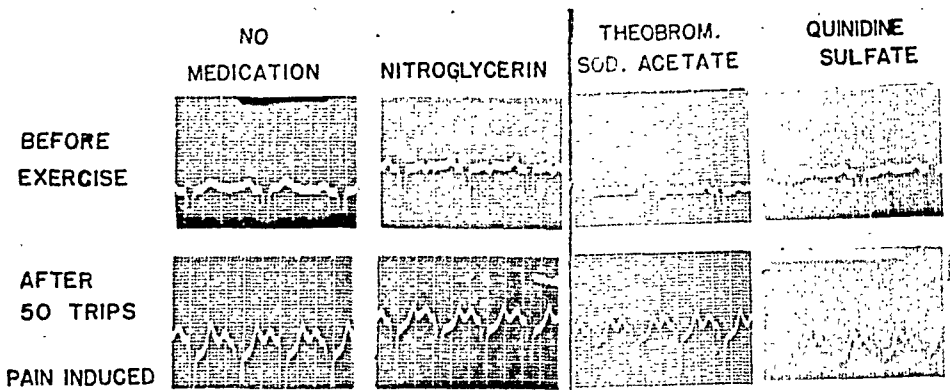


Fig. 2.—No response to medication (Group III), as illustrated by results on Patient B. A. When no medication was administered, fifty trips caused pain and an average depression of the initial portion of the S-T segment of 4.0 mm. The same results were obtained after the administration of nitroglycerin, theobromine sodium acetate, and quinidine sulfate.

Results With Theobromine Sodium Acetate

The effect of theobromine sodium acetate was studied on thirteen patients (Table III). Four showed a marked response to the drug (Group I). They were able to do at least 50 per cent more work before developing pain; the average depression of the S-T segment after exercise in these cases was 1.7 mm. before medication and 0.1 mm. after medication (Fig. 3).

Group II consisted of seven patients who did not develop angina on performing the same amount of exercise that produced pain when no medication was taken. The average S-T segment depression after exercise was 2.6 mm. when no drug was taken and 1.7 mm. after medication.

The remaining two patients (Group III) were unable to do more work after medication, and showed the same depression of the S-T segment that they had when no drug was taken (Fig. 2).

TABLE III

OBJECTIVE EVIDENCE OF THE EFFICACY OF THEOBROMINE SODIUM ACETATE IN PATIENTS WITH ANGINA PECTORIS

PATIENT	NO MEDICATION†		THEOBROMINE SODIUM ACETATE					
			NO INCREASE* IN WORK		50% INCREASE* IN WORK		100% INCREASE* IN WORK	
	NO. OF TRIPS	S-T SEG- MENT DEPRES- SION (MM.)	NO. OF TRIPS	S-T SEG- MENT DEPRES- SION (MM.)	NO. OF TRIPS	S-T SEG- MENT DEPRES- SION (MM.)	NO. OF TRIPS	S-T SEG- MENT DEPRES- SION (MM.)
<i>Group I. S-T Changes Diminished Markedly Following Medication</i>								
S. R.	51	2.7	51†	0.2	66	3.5		
H. Shr.	22	1.5	26†	0.3	40†		50†	0.8
S. L.	26	1.5	26†	0.0			53	1.0
R. C.	26	1.0	26†	0.0	42†	1.0		
<i>Group II. S-T Changes Diminished Moderately Following Medication</i>								
M. B.	36	3.0	36†	2.4				
S. E.	27	2.7	27†	2.3				
H. Shl.	54	2.5	54†	1.6	74	2.8		
B. L.	18	2.3	18†	1.0				
M. L.	40	1.8	40†	0.7	54	1.0		
P. R.	49	3.5	49†	2.5				
L. W.	36	2.7	36†	1.5	55†	3.5		
<i>Group III. S-T Changes Not Prevented by Medication</i>								
S. W.	38	1.7	38†	1.7	50†	2.8		
B. A.	50	4.0	50	4.0				

*Increase in work as compared with the amount necessary to induce pain when no medication was given.

†No attack of angina was induced.

‡Exercise was continued until attack was produced.

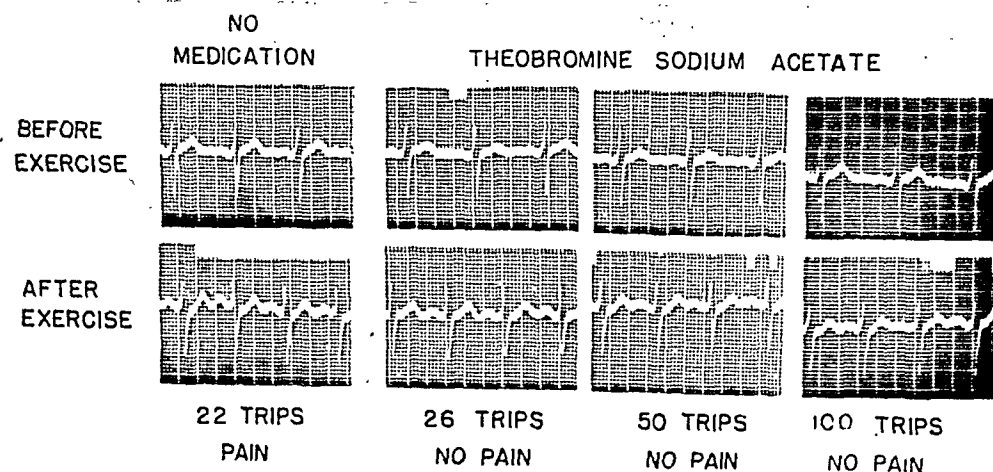


Fig. 3.—Marked response to theobromine sodium acetate (Group I), as illustrated by results on Patient H. Shr. When no medication was given, twenty-two to twenty-six trips produced angina and caused an average depression of the S-T segment of 1.5 mm. After medication, the same amount of work induced no pain and an S-T segment depression of 0.3 mm; after 100 per cent and 300 per cent more exercise no pain was induced and the S-T segment was depressed less than 1.0 mm.

TABLE IV

OBJECTIVE EVIDENCE OF THE EFFICACY OF QUINIDINE SULFATE IN PATIENTS WITH ANGINA PECTORIS

PATIENT	NO MEDICATION**		QUINIDINE SULFATE					
			NO INCREASE§ IN WORK		50% INCREASE§ IN WORK		100% INCREASE§ IN WORK	
	NO. OF TRIPS	S-T SEG- MENT DEPRES- SION (MM.)	NO. OF TRIPS	S-T SEG- MENT DEPRES- SION (MM.)	NO. OF TRIPS	S-T SEG- MENT DEPRES- SION (MM.)	NO. OF TRIPS	S-T SEG- MENT DEPRES- SION (MM.)
<i>Group I. S-T Changes Diminished Markedly Following Medication</i>								
M. L.	40	1.8	40†	0.0	60	0.5		
H. Shr.	22	1.5	22†	0.0	*		40†	0.8
S. L.	26	1.5	26†	0.5	40*	1.2		
R. C.	26	1.0	26†	0.0	*		47	1.0
<i>Group II. S-T Changes Diminished Moderately Following Medication</i>								
M. B.	36	3.0	36†	1.6				
S. E.	27	2.7	27†	1.0	39††	1.5		
S. R.	51	2.7	51†	1.3	64††	1.5		
H. Shl.	54	2.5	54†	1.0	64††	1.3		
P. R.	49	3.5	47	2.0				
<i>Group III. S-T Changes Not Prevented by Medication</i>								
L. W.	36	2.7	36†	2.7				
S. W.	38	1.7	38†	2.3				
B. A.	50	4.0	50	3.5				

*No pain on performing 50 per cent more work than was possible when no medication was taken.

†No attack of angina induced.

‡No pain—patient stopped because of fatigue before performing 50 per cent more work than was possible when no medication was taken.

§Increase in work as compared with the amount necessary to induce pain when no medication was given.

**Exercise was continued until attack was produced.

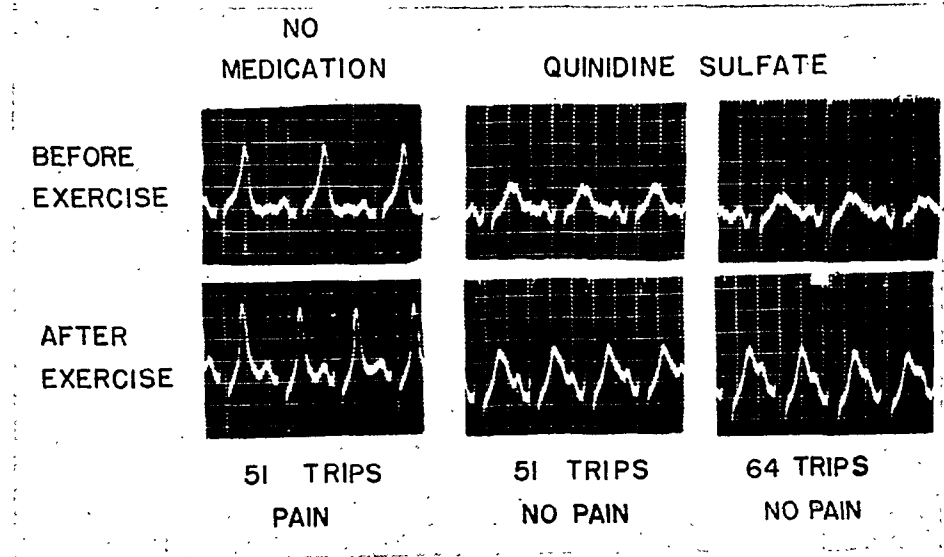


Fig. 4.—Moderate response to quinidine sulfate (Group II), as illustrated by results on Patient S. R. When no medication was administered, fifty-one trips over the two-step staircase induced an attack of angina and caused a depression of the S-T segment of 2.7 mm. After the administration of quinidine sulfate, an increased amount of work caused no pain and only 1.5 mm. depression of the S-T segment.

Results With Quinidine Sulfate

The effect of quinidine sulfate was studied on twelve patients (Table IV). Four showed a marked response, five, a moderate response, and three, no response. After exercise the average depression of the S-T segment of subjects in Group I was 1.5 mm. when no medication was taken, and 0.1 mm. after quinidine therapy. In Group II the average depression without medication was 2.9 mm., and, following medication, 1.4 mm. (Fig. 4). The average depression of the S-T segment of patients in Group III was 2.8 mm. when no medication was taken, and 2.8 mm. after the administration of the drug (Fig. 2).

After the administration of quinidine sulfate the electrocardiograms uniformly showed a prolongation of electrical systole (as measured from the beginning of the Q to the end of the T waves). This phenomenon has been recognized for some time.²⁷⁻²⁹ The beneficial effects of quinidine were not dependent on this phenomenon, however, for prolongation of the Q-T interval occurred to the same degree in all patients (Figs. 2 and 4), irrespective of an increased ability to exercise after taking the drug.

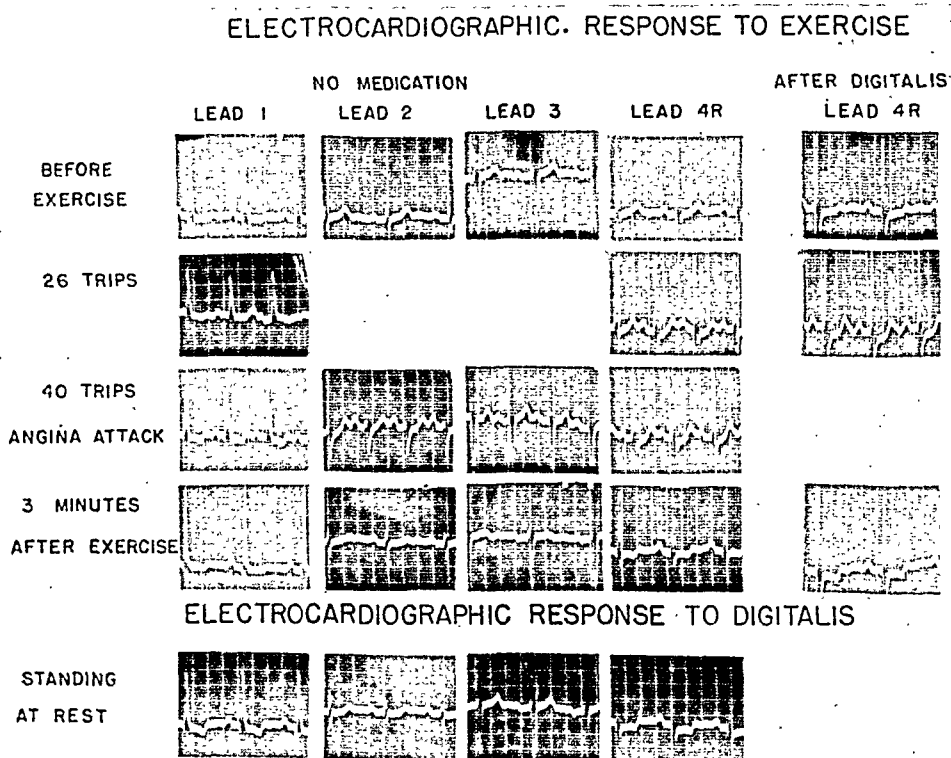


Fig. 5.—Patient M. L. Electrocardiographic response to digitalis and to exercise before and after the administration of digitalis.

Results With Digitalis

Studies on digitalis were discontinued because all three patients developed a marked increase in the frequency and the severity of their attacks of angina in daily life. After the administration of digitalis,

less work could be performed under standardized conditions before pain developed, and the electrocardiographic changes under such conditions were much more marked than those which occurred when no medication was given. Furthermore, following digitalis, the electrocardiogram with the patient standing at rest showed changes similar to those observed after exercise when no medication was given.

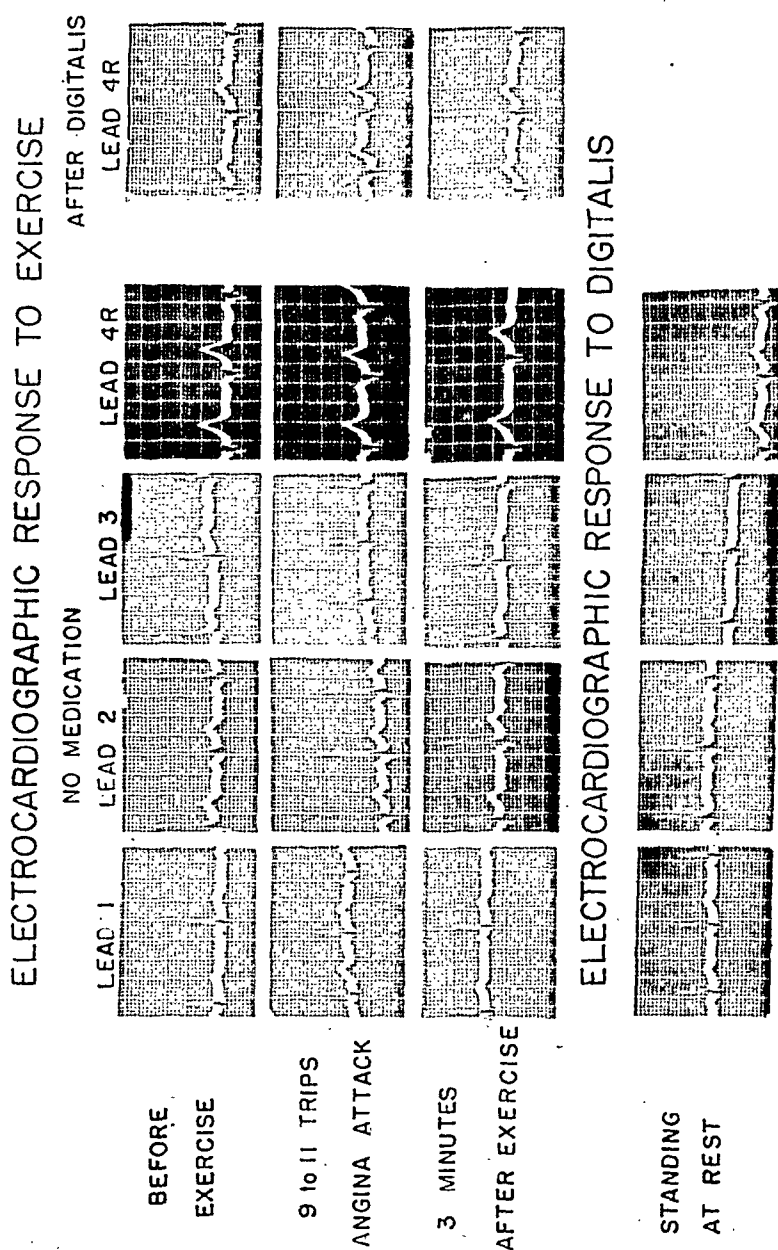


Fig. 6.—Patient N. B. Electrocardiographic response to digitalis and to exercise before and after the administration of digitalis.

Patient M. L. (Fig. 5) usually experienced one to two attacks each week, and his exercise tolerance was approximately forty trips. Beginning with the second day of digitalis therapy (after he had received 0.6 Gm.), he experienced several attacks of pain daily and complained of a constant sense of substernal pressure. He refused to con-

tinued digitalis therapy after taking 1.4 Gm. in five days, and, at that time, on performing twenty-six trips, he developed an attack more severe and about twice as long as usual. Before medication, exercise caused a definite depression of the S-T segment in Leads I, II, and IV, but Lead III showed few changes. After digitalis, Lead I, taken

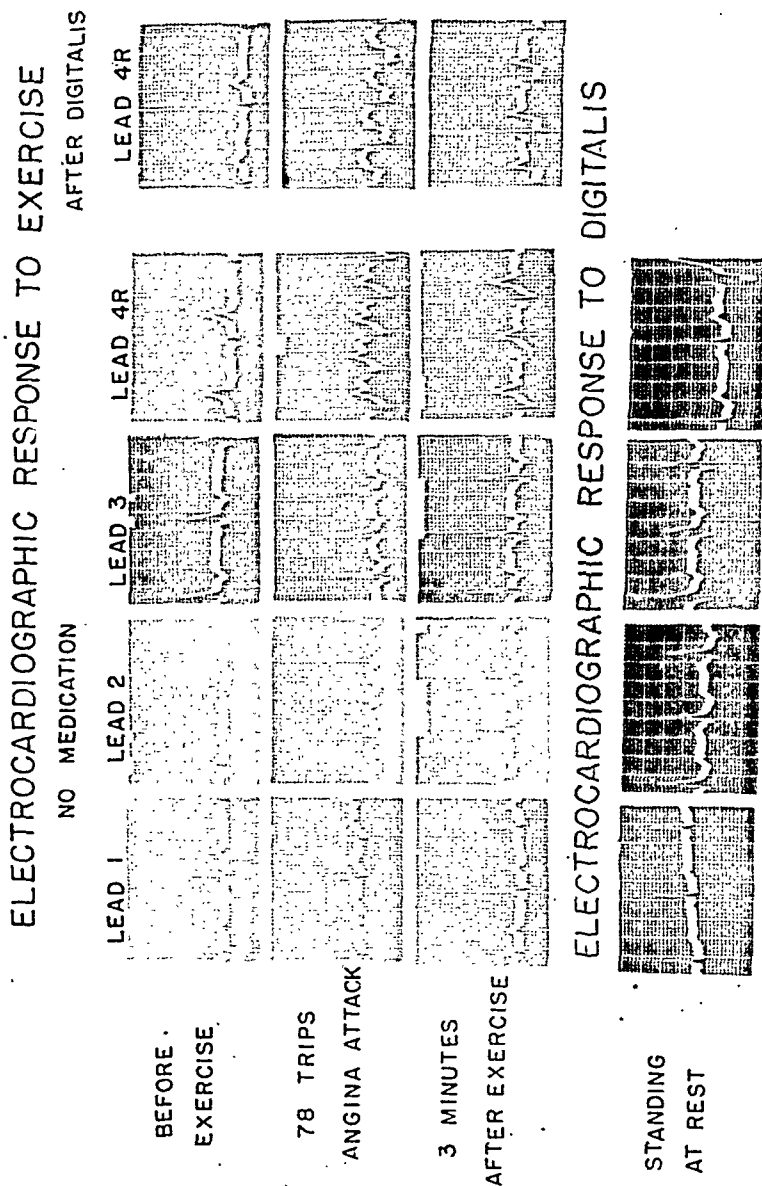


Fig. 7.—Patient H. B. Electrocardiographic response to digitalis and to exercise before and after the administration of digitalis.

with the patient standing at rest, was similar to Lead I immediately after the cessation of exercise when no medication was given; Lead IV was similar to that obtained three minutes after exercise; and Leads II and III showed no significant changes. After digitalis the electrocardiographic changes induced by twenty-six trips were greater than those observed after forty trips when no medication was given.

Patient N. B. (Fig. 6), during more than one and one-half years of observation, always developed an attack of one and one-half minutes' duration after eleven trips; he had been experiencing one to three attacks daily. After approximately one-half the digitalizing dose had been administered (0.6 Gm. in two days), he experienced an increase in pain during daily life. After receiving 1.4 Gm. of digitalis in five days the most severe attack that he had ever experienced (three and one-half minutes in duration) was induced by nine trips. The electrocardiographic changes during attacks induced by the small amount of work which could be performed without medication were minimal, and, therefore, the electrocardiographic response to vasodilating drugs was not studied. After the administration of digitalis the electrocardiogram (with the patient standing at rest) also showed minimal changes, except for a slight concavity in the S-T segment of Lead IV. Exercise after digitalis, however, produced marked changes, especially in the S-T segment of Lead IVR.

Patient H. B.'s reaction to vasodilating drugs was not studied because his attacks occurred rarely (less than once a week). Beginning with the third day of digitalis (1.0 Gm.) therapy, he experienced several attacks of pain daily. After exercise (Fig. 7), when no medication was given, Leads II and III showed little change, but in Leads I and IV there was a depression of the first portion of the S-T segment (1.5 and 2.8, respectively). After digitalis, with the patient standing at rest, similar though less striking changes were observed. Because of the marked increase in pain, exercise with electrocardiographic studies was not performed until four days after digitalis had been discontinued. At this time no pain was produced by the usual amount of exercise (seventy-eight trips); the test was stopped because of the marked electrocardiographic changes.

COMMENT

It is apparent from the above studies that the administration of nitroglycerin, theobromine sodium acetate, or quinidine sulfate enables some patients with angina pectoris to do a measurably greater amount of work under standardized conditions, and, at the same time, prevents the changes in the S-T segment which result from exercise; the administration of inert drugs has no such effect. The administration of digitalis to some patients with angina pectoris results in an increased frequency of attacks in daily life, a decrease in the amount of work which can be performed under standardized conditions, an increase in electrocardiographic changes following exertion, and changes in the electrocardiogram (taken with the patient standing at rest) similar to those observed after exercise without medication. These results show that the administration of nitroglycerin, theobromine sodium acetate, or quinidine sulfate in the dosage and manner customarily employed in the

treatment of such patients is of definite therapeutic value, whereas the administration of digitalis is harmful to some patients with angina pectoris.

These conclusions are in accord with the clinical experience of generations of physicians and patients, with the vast bulk of experimental evidence obtained on laboratory animals, and also with the objective electrocardiographic studies of Goldhammer and Scherf¹⁹ and Levy, Brueni, and Williams^{22, 23} on patients with coronary artery disease, and with those of Zwillinger³⁰ on normal young subjects.

The present studies differ from previous investigations in that the conditions of the experiments resemble closely the clinical conditions under which attacks of angina pectoris occur in man; the drugs were administered to patients with angina in the customary therapeutic manner and dosage; the use of exercise to precipitate angina reproduces the conditions which induce attacks in daily life; and the electrocardiographic changes closely resemble those which occur consistently during attacks of angina pectoris.

The results and conclusions of the present investigation are not in accord with the careful clinical studies of Evans and Hoyle⁸ and Gold, Kwit, and Otto.¹¹ The experiments of these investigators were controlled so carefully that the results cannot be dismissed unless adequate reason can be found for the discrepancy between their results and those of practically all other investigators. There is reason to believe that this discrepancy is due to the difficulties of evaluating the results of therapy in angina by purely clinical or subjective methods. In the last analysis, all such clinical evaluation depends on the ability of the patient and the investigator to differentiate between improvement resulting from medication and apparent improvement unrelated to therapy. It is not unusual for untreated patients to be free of pain for many days, and we have observed spontaneous remissions of a month or longer. Many factors, which are difficult to recognize, may cause this apparent improvement; these include a decrease in physical or emotional activity, a rise in the prevailing temperature, smaller and more digestible meals, and the beneficial psychologic effect of sympathetic medical supervision. Statistical clinical evaluation of the efficacy of treatment is further complicated by the fact that a large percentage (probably between 30 and 40 per cent) of patients with angina pectoris do not respond to any of the drugs in use today, and that the frequency of their attacks may vary spontaneously during investigation.

It was because of these difficulties that measurements of the patients' ability to exercise under standardized conditions were resorted to in these and previous studies.^{13, 14, 24, 25, 31-34} The results of these measurements agree closely with the clinical response to therapy and are of considerable aid in differentiating between real and apparent improvement. Patients who are able to perform an appreciably greater amount

of exercise after medication usually experience a marked decrease in the frequency of attacks of pain in daily life; investigation of the daily routine of patients who show similar clinical improvement without an increased exercise tolerance usually reveals causes other than medication for the apparent improvement.

The methods used in this study are of considerable practical import. Many drugs have been placed on the market for the treatment of angina pectoris without adequate evidence of their efficacy. It is self-evident that the administration of inert or harmful drugs to patients with angina is dangerous and should be avoided by both the medical profession and the pharmaceutical houses. The simplicity of the methods used in this study, together with the direct clinical applicability of their results, suggests the advisability of requiring similar biologic assays of all drugs advocated for use in the treatment of angina pectoris.

The present and previous reports^{13, 14, 24, 31, 34, 111} indicate that an evaluation of the efficacy of medication in the treatment of angina pectoris should include (1) *the incidence and degree of beneficial effects* (measured by the patient's ability to perform work under standardized conditions after administration of the drug in the dosage and manner usually employed in the treatment of angina pectoris), (2) *adequate control studies* (carried out in a fashion identical with the above, using both disguised medication and inert preparations of similar appearance), (3) *careful comparison of these results with the clinical response* (as estimated by the frequency of attacks in daily life while taking the drug, keeping in mind that apparent improvement may occur under medical supervision), (4) *objective electrocardiographic studies on patients, to confirm these results* (these objective studies should include the prevention of S-T segment changes associated with an increased ability to perform work in patients who are benefited by the drug, and the persistence of such S-T changes in patients who cannot increase their exercise tolerance after medication. Such objective electrocardiographic studies will reveal little if the action of the therapeutic agent depends on its analgesic properties, e.g., cobra venom or alcohol injection of the sensory pathways,³⁵ (5) *studies of the toxic effects of the drug* and a determination of the optimal dose, and (6) *comparison of the efficacy of the drug with that of other drugs* (especially nitroglycerin) which are commonly used in the treatment of angina pectoris.

An illustration of the practical use of this method in the evaluation of octyl nitrite is being reported.³¹

The results of the present investigation are in accord with the anoxemia theory of the production of angina attacks, and with the experimental evidence obtained on animals which indicates that the nitrites and purines are coronary vasodilators, whereas digitalis occasionally acts as a coronary vasoconstrictor. The deviation of the initial portion

of the S-T segment is apparently produced by myocardial anoxia, for it appears on breathing an atmosphere of low-oxygen content,^{24, 36} and can be prevented by breathing pure oxygen before and during exercise.²⁴ Furthermore, these S-T changes are qualitatively, and frequently quantitatively, similar to those in clinical and experimental coronary arterial occlusion, when myocardial anoxia is known to exist. The prevention of the S-T changes during exercise suggests, therefore, that the drug has a vasodilating action on the coronary arteries, whereas the development or accentuation of changes may indicate a vasoconstricting action. Since patients with angina pectoris of arteriosclerotic origin suffer pain during exercise because of an inadequate flow of oxygenated arterial blood, rather than because of any unusual degree of arterial oxygen unsaturation, it is not surprising that the administration of the vasodilating drugs is more effective than breathing pure oxygen in preventing angina and the electrocardiographic changes induced by exercise.

SUMMARY AND CONCLUSIONS

When patients with angina pectoris exercise under standardized conditions, the amount of work which can be done before pain is induced is relatively constant for each person. Precordial lead electrocardiograms (IVR) taken before and *immediately after* exertion under these conditions show a change (usually a depression) in the level of the initial portion of the S-T segment, the magnitude of which is relatively constant for each subject.

When patients with angina pectoris are given nitroglycerin, theobromine sodium acetate, or quinidine sulfate, in the dosage and in the manner frequently employed in the treatment of this condition, many of the patients (more than one-half of the present series) are able to do more work under standardized conditions before pain is induced and show strikingly less change in the electrocardiogram. This increase in exercise tolerance is accompanied by a corresponding decrease in the frequency of attacks in daily life.

When the same patients are given lactose or sodium bicarbonate which has been disguised to resemble theobromine sodium acetate or quinidine sulfate, no increase in exercise tolerance occurs and the electrocardiographic changes are as great as when no medication is given. The clinical response to these inert drugs varies; apparent improvement may or may not occur, depending on conditions other than medication.

When patients with angina pectoris are given digitalis, an increase in the frequency and severity of cardiac pain sometimes occurs (in all three of the cases in the present series). This is accompanied by a decrease in the amount of work which can be done under standardized conditions, an increase in the electrocardiographic changes induced by work, and the development of changes in the electrocardiogram while

the patient stands at rest which resemble, in many respects, the electrocardiographic changes induced by exercise when no medication is taken.

The methods used in this study afford an objective means of testing the efficacy of drugs which are used in the treatment of angina pectoris under conditions closely comparable to actual clinical conditions. The results obtained by these methods yield objective evidence that nitroglycerin, theobromine sodium acetate, quinidine sulfate, and digitalis exert a specific effect on the heart.

REFERENCES

1. Council of Pharmacy and Chemistry: Limitations of Claims for Aminophylline and Other Xanthine Derivatives, *J. A. M. A.* 108: 2203, 1937.
2. Council of Pharmacy and Chemistry: Therapeutic Claims for Theobromine and Theophylline Preparations, *J. A. M. A.* 94: 1306, 1930.
3. Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Studies on the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis and Myocardial Infarction to the Pathologic Findings, *AM. HEART J.* 19: 1, 1940.
4. Schlesinger, M. J.: An Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, *AM. HEART J.* 15: 528, 1938.
5. Askanazy, S.: Klinisches über Diuretin, *Deutsche Arch. f. klin. Med.* 56: 209, 1896.
6. Gilbert, N. C., and Kerr, J. A.: Clinical Results in Treatment of Angina Pectoris With the Purine Base Diuretics, *J. A. M. A.* 92: 201, 1929.
7. Smith, F. M., Rathe, H. W., and Paul, W. P.: Theophylline in the Treatment of Disease of the Coronary Arteries, *Arch. Int. Med.* 56: 1250, 1935.
8. Evans, W., and Hoyle, C.: The Comparative Value of Drugs Used in the Continuous Treatment of Angina Pectoris, *Quart. J. Med., New Series* 2: 311, 1933.
9. Master, A. M.: Treatment of Coronary Thrombosis and Angina Pectoris, *M. Clin. North America* 19: 873, 1935.
10. Master, A. M., Jaffe, H. L., and Dack, S.: The Drug Treatment of Angina Pectoris Due to Coronary Artery Disease, *Am. J. M. Sc.* 197: 774, 1939.
11. Gold, H., Kwit, N. T., and Otto, H.: The Xanthines (Theobromine and Aminophylline) in the Treatment of Cardiac Pain, *J. A. M. A.* 108: 2173, 1937.
12. Massell, H. M.: Clinical Observations on the Value of Various Xanthine Derivatives in Angina Pectoris, *J. Lab. & Clin. Med.* 24: 380, 1939.
13. Brown, M. G., and Riseman, J. E. F.: The Comparative Value of Purine Derivatives in the Treatment of Angina Pectoris, *J. A. M. A.* 109: 256, 1937.
14. Riseman, J. E. F., and Brown, M. G.: Medicinal Treatment of Angina Pectoris, *Arch. Int. Med.* 60: 100, 1937.
15. Wayne, E. J., and Laplace, L. B.: Observations on Angina of Effort, *Clin. Sc.* 1: 103, 1933.
16. Missal, M.: Exercise Tests and the Electrocardiogram in the Study of Angina Pectoris, *Ann. Int. Med.* 11: 2018, 1938.
17. Kisch, F.: Nitroglyzerinschutz der Angina Pectoris, *Med. Klin.* 31: 1133, 1935.
18. Proger, S. H., Minnich, W. R., and Magendantz, H.: The Circulatory Response to Exercise in Patients With Angina Pectoris, *AM. HEART J.* 10: 511, 1935.
19. Goldhammer, St., and Scherf, D.: Elektrokardiographische Untersuchungen bei Kranken mit Angina Pectoris ("Ambulatorische Typus"), *Ztschr. f. klin. Med.* 122: 134, 1932.
20. Larsen, K. H.: Om Forandringer, I Elektrokardiogrammet Hos sunde Og Syge under Experimentel Iltmangel, Copenhagen, 1938, Enjar Munksgaards Forlag.
21. Raab, W., and Schönbrunner, E.: Die Normalisierungstendenz des Elektrokardiogramms nebennierenbestrahlter Angina Pectoris Kranker, *Arch. f. Kreislaufforsch.* 4: 362, 1939.

22. Levy, R. L., Bruenn, H. G., and Williams, N. E.: Effects of Induced Anoxemia in Patients With Coronary Sclerosis, as Modified by Certain Drugs, *Tr. A. Am. Physicians* 54: 244, 1939.
23. Levy, R. L., Bruenn, H. G., and Williams, N. E.: The Modifying Action of Certain Drugs (Aminophyllin, Nitrites, Digitalis) Upon the Effects of Induced Anoxemia in Patients With Coronary Insufficiency, *AM. HEART J.* 19: 639, 1940.
24. Riseman, J. E. F., Waller, J. V., and Brown, M. G.: The Electrocardiogram During Attacks of Angina Pectoris; Its Characteristics and Diagnostic Significance, *AM. HEART J.* 19: 683, 1940.
25. Riseman, J. E. F., and Stern, B.: A Standardized Exercise Tolerance Test for Patients With Angina Pectoris on Exertion, *Am. J. M. Sc.* 188: 646, 1934.
26. Eggleston, C.: Administration of Digitalis by the "Eggleston Method," *J. A. M. A.* 74: 733, 1920.
27. Aschenbrenner, R.: Über das Digitalis—Elektrokardiogramm, *Klin. Wehnschr.* 15: 1039, 1936.
28. Landau, N.: Über die Verlängerung der Systole bei Tetanie und ihre Beeinflussung durch verschiedene Pharmaca, *Klin. Wehnschr.* 17: 93, 1938.
29. Miki, Y.: Experimentelle und klinische Untersuchungen über die Dauer des K-EKG (Kammer-Elektrokardiogramm), *Ztschr., f. d. ges. exper. Med.* 27: 323, 1922.
30. Zwilling, L.: Die Digitaliseinwirkung auf das Arbeitselektrokardiogramm, *Med. Klin.* 31: 977, 1935.
31. Freedberg, A. S., Spiegl, E. D., and Riseman, J. E. F.: Octyl Nitrite in the Treatment of Angina Pectoris, *AM. HEART J.* 22: 519, 1941.
32. Riseman, J. E. F., and Brown, M. G.: The Duration of Attacks of Angina Pectoris on Exertion and the Effect of Nitroglycerin and Amyl Nitrite, *New England J. Med.* 217: 470, 1937.
33. Riseman, J. E. F., and Brown, M. G.: An Analysis of the Diagnostic Criteria of Angina Pectoris, *AM. HEART J.* 14: 331, 1937.
34. Riseman, J. E. F., and Brown, M. G.: The Effect of Oxygen on the Exercise Tolerance of Patients With Angina Pectoris, *AM. HEART J.* 18: 150, 1939.
35. Freedberg, A. S., Riseman, J. E. F., and Spiegl, E. D.: Unpublished data.
36. Rothschild, M. A., and Kissin, M.: Induced General Anoxemia Causing S-T Deviation in the Electrocardiogram, *AM. HEART J.* 8: 45, 1933.
37. Voegtlin, C., and Macht, D. I.: The Action of Nitrites and Drugs of the Digitalis Group on the Isolated Coronary Artery, *J. Pharmacol. & Exper. Therap.* 5: 77, 1913.
38. Cow, D.: Some Reactions of Surviving Arteries, *J. Physiol.* 42: 125, 1911.
39. Loeper, M., Mongeot, A., and Aubertot, V.: Etude critique et experimentale de dix medicaments hypotensure et de leur action sur en Tonicite myocardique, *Presse méd.* 42: 857, 1934.
40. Pal, J.: Ueber toxische Reaktionen der Koronararterien und Bronchien, *Deutsche med. Wehnschr.* 38: 5, 1912.
41. Krantz, J. C., Jr., Carr, C. J., and Forman, S. E.: Alkyl Nitrites. II. The Pharmacology of 2-Ethyl-n-Hexyl-1-Nitrite, *J. Pharmacol. & Exper. Therap.* 64: 302, 1938.
42. Kountz, W. B.: Studies on the Coronary Arteries of the Human Heart, *J. Pharmacol. & Exper. Therap.* 45: 65, 1932.
43. Eppinger, H., and Hess, L.: Versuche über die Einwirkung von Arzneimitteln auf überlebende Coronargefäße, *Ztschr. f. exper. Path. und Therap.* 5: 622, 1909.
44. Mikuliczisch, zitiert von Loewi, O.: Ueber Digitalis Therapie, *Mitt. des Verein der Aerzte in Steirmark Graz.* 48: 379, 1911.
45. Lange, F.: Über die blutdrucksenkende Wirkung gewisser Organextrakte, *Arch. f. exper. Path. u. Pharmacol.* 164: 417, 1932.
46. Cruickshank, E. W. H., and SubbaRau, A.: Reactions of Isolated Systemic and Coronary Arteries, *J. Physiol.* 64: 65, 1927.
47. Krawkow, N. P.: Über die Wirkung der Gifte auf die Kranzgefäße des Herzen, *Pflüger's Arch. f. d. ges. Physiol.* 157: 501, 1914.
48. Barbour, H. G.: Note on the Action of Histamin Upon Surviving Arteries, *J. Pharmacol. & Exper. Therap.* 4: 245, 1913.
49. Anrep, G. V.: The Regulation of the Coronary Circulation, *Physiol. Rev.* 6: 619, 1926.

50. Rothlin, E.: Experimentelle Untersuchungen über die Wirkungsweise einiger vasotonisierender Substanzen organischer Natur auf überlebende Gefässe, *Biochem. Ztschr.* 111: 299, 1920.
51. Wedd, A. M., and Fenn, W. O.: The Action of Cardiac Musculature and the Vagomimetic Behavior of Adenosine, *J. Pharmacol. & Exper. Therap.* 47: 365, 1933.
52. Meyer, O. B.: Über einige Eigenschaften der Gefässmuskulatur mit besonderer Berücksichtigung der Adrenalwirkung, *Ztschr. f. Biol.* 48: 352, 1906.
53. Pal, J.: Über die Gefässwirkung des Hypophysenextraktes, *Wien. med. Wchnschr.* 59: 138, 1909.
54. Pal, J.: Zur Kenntnis der Wirkung des Hypophysenextraktes auf isolierte Blutgefässe, *Zentralbl. f. Physiol.* 23: 253, 1909.
55. Gunn, J. A.: The Action of Histamine on the Heart and Coronary Vessels, *J. Pharmacol. & Exper. Therap.* 29: 325, 1926.
56. Katz, L. N., and Lindner, E.: The Reaction of the Coronary Vessels to Drugs and Other Xanthine Derivatives, *J. A. M. A.* 113: 2116, 1939.
57. Katz, L. N., Lindner, E., Weinstein, W., Abramson, D. I., and Jochim, K.: Effect of Various Drugs on the Coronary Circulation of the Denervated Isolated Heart of the Dog and Cat, *Arch. internat. de pharmacodyn. et de therap.* 59: 399, 1938.
58. Smith, F. M., Miller, G. H., and Graber, V. C.: The Effect of Caffeine Sodium Benzoate, Theobromine Sodium Salicylate, Theophyllin and Euphyllin on the Coronary Flow and Cardiac Action of the Rabbit, *J. Clin. Investigation* 2: 157, 1925.
59. Loeb, O.: Über die Beeinflussung des Koronarkreislaufs durch einige Gifte, *Arch. f. exper. Path. u. Pharmacol.* 51: 64, 1903.
60. Bodo, R.: The Effect of the "Heart Tonics" and Other Drugs Upon the Heart-Tone and Coronary Circulation, *J. Physiol.* 64: 365, 1927.
61. Kountz, W. B., and Smith, J. R.: The Flow of Blood in the Coronary Arteries in Pathological Hearts, *J. Clin. Investigation* 17: 147, 1936.
62. Wedd, A. M.: The Action of Adenosine and Certain Related Compounds on the Coronary Flow of the Perfused Heart of the Rabbit, *J. Pharmacol. & Exper. Therap.* 41: 355, 1931.
63. Fowler, W. M., Hurevitz, H. M., and Smith, F. M.: Effect of Theophylline Ethylenediamine on Experimentally Induced Cardiac Infarction in the Dog, *Arch. Int. Med.* 56: 1242, 1935.
64. Heathecotte, R. St. A.: The Action of Caffeine, Theobromine and Theophylline on the Mammalian and Batrachian Heart, *J. Pharmacol. & Exper. Therap.* 16: 327, 1920.
65. LeRoy, G. V., Fenn, G. K., and Gilbert, N. C.: Personal communication.
66. Krawkow, N. P.: Über die funktionellen Eigenschaften der Blutgefässe isolierter (normal und pathologischer) Organe von Tieren und Menschen, *Ztschr. f. d. ges. exper. Med.* 27: 127, 1922.
67. Woichansky, D.: Vergleich der Wirkung einiger Stoffe auf die Coronargefässe und die peripheren Gefässe isolierter Kaninchenorgane, *Ztschr. f. d. ges. exper. Med.* 83: 429, 1932.
68. Guggenheimer, H., and Sassa, K.: Über die Beeinflussung des Coronar-kreislaufs durch Purinderivate, *Klin. Wchnschr.* 2: 1451, 1923.
69. Fisher, I., Guggenheimer, H., and Müller, E. A.: Ueber die Beeinflussung von Koronardurchblutung und Herztonus durch Theophyllin Präparate und Strophanthin nach Untersuchungen am Starlingschen Herz-Lungen Präparate, *Deutsche med. Wchnschr.* 54: 1584, 1928.
70. Iwai, M., and Sassa, K.: Über die Beeinflussung des Koronarkreislaufs durch Purinderivate, *Arch. f. exper. Path.* 99: 215, 1923.
71. Stoland, O. O., Ginsburg, A. M., Loy, D. L., and Hiebert, P. E.: Studies on Coronary Circulation. IV. A. The Duration of the Coronary Dilator Action of Theophylline Ethylene-diamine, *J. Pharmacol. & Exper. Therap.* 51: 387, 1934.
72. Davis, J. C.: Effect of Aminophyllin on the Coronary Capillary Blood Flow, *J. Clin. Investigation* 17: 511, 1938.
73. Anrep, G. V., and Stacey, R. S.: Comparative Effects of Various Drugs Upon the Coronary Circulation, *J. Physiol.* 64: 187, 1927.
74. Anitschkow, S. W.: Über die Wirkung von Giften auf die Coronargefässe des isolierten Menschenherzens bei verschiedenen Erkrankungen, *Ztschr. f. d. ges. exper. Med.* 36: 236, 1923.
75. Hedbom, K.: Ueber die Einwirkung verschiedener Stoffe auf das isolierte Säugethierherz, *Skandinav. Arch. f. Physiol.* 8: 169, 1898.

76. Deneke, T., and Adam, H.: Beobachtungen am isolierten überlebenden menschlichen Herzen, *Ztschr. f. exper. Path. u. Therap.* 2: 491, 1905.
77. Wesse, H.: *Digitalis*, Leipzig, 1936, Georg Thieme.
78. Rabe, F.: Die Reaction der Kranzgefäße auf Arzneimittel, *Ztschr. f. exper. Path. u. Therap.* 11: 175, 1912.
79. Starr, I., Jr.: A Note on the Antagonism between the Cardiac Action of Acetyl- β -Methyl-Choline and Acetyl Choline and that of Quinidine, *J. Pharmacol. & Exper. Therap.* 56: 77, 1936.
80. Narayana, B.: Vaso-constrictors et Vaso-dilatateurs coronaires, *Compt. rend. Soc. de biol.* 114: 550, 1933.
81. Müller, E. A., Salomon, H., and Suelzer, G.: Die Wirkung von Histamin auf Herz und Lungen, *Arch. f. exper. Path.* 164: 441, 1932.
82. Fisher, I., Müller, E. A., and Suelzer, G.: Der Einfluss des Eutons auf das isolierte Säugetierherz, *Med. Klin.* 24: 576, 1928.
83. Frey, E. K., and Kraut, H.: Ein neues Kreislaufhormon und seine Wirkung, *Arch. f. exper. Path. u. Pharmacol.* 133: 1, 1928.
84. Haberlandt, L.: *Das Hormone der Herzbewegung*, Berlin, 1927, Urban & Schwarzenberg.
85. Meyer, F.: Ueber die Wirkung verschiedener Arzneimittel auf die Coronargefäße des lebenden Tieres, *Arch. f. d. ges. Physiol.* 223, 1912.
86. Bond, G. S.: Effect of Various Agents on the Blood Flow Through Arteries and Veins, *J. Exper. Med.* 12: 575, 1910.
87. Schloss, K.: Über die Wirkung der Nitrite auf die Durchblutung des Herzens (Versuche am Herzen in Situ), *Deutsche Arch. f. klin. Med.* 111: 310, 1913.
88. Wégria, R., Essex, H. E., Herrick, J. F., and Mann, F. C.: The Simultaneous Action of Certain Drugs on the Blood Pressure and on the Flow in the Right and Left Coronary Arteries, *AM. HEART J.* 20: 557, 1940.
89. Essex, H. E., Wégria, R. E., Herrick, J. F., and Mann, F. C.: The Effect of Certain Drugs on the Coronary Blood Flow of the Trained Dog, *AM. HEART J.* 19: 554, 1940.
90. Essex, H. E., Herrick, J. F., Baldes, E. J., and Mann, F. C.: Blood Flow in the Circumflex Branch of the Left Coronary Artery of the Intact Dog, *Am. J. Physiol.* 117: 271, 1936.
91. Francois-Franc, C. A.: Effet vaso-dilatateur du nitrate d'amyle sur les vaisseaux de l'écorce cérébrale et sur les vaisseaux du myocarde, *Compt. rend. Soc. de biol.* 55: 1448, 1903.
92. Smith, F. M., and Miller, G. H.: A Study of the Action of Theophyllin and Theobromin on the Coronary Circulation of the Intact Heart, *Am. J. Physiol.* 85: 407, 1928.
93. Gilbert, N. C., and Fenn, G. K.: The Effect of the Purine Base Diuretics on the Coronary Flow, *Arch. Int. Med.* 44: 118, 1929.
94. Sakai, S., and Saneyoshi, S.: Über die Wirkung einiger Herzmittel auf die Coronargefäße, *Arch. f. exper. Path.* 78: 331, 1915.
95. Gilbert, N. C., and Fenn, G. K.: Effect of Digitalis on the Coronary Flow, *Arch. Int. Med.* 50: 668, 1932.
96. Fenn, G. K., and Gilbert, N. C.: Anginal Pain as a Result of Digitalis Administration, *J. A. M. A.* 98: 99, 1932.
97. Essex, H. E., Herrick, J. F., Baldes, E. J., and Mann, F. C.: Digitalis and Coronary Blood Flow, *Proc. Soc. Exper. Biol. & Med.* 38: 325, 1938.
98. Rühl, A.: Über Herzinsuffizienz durch Histamin, *Arch. f. exper. Path. u. Pharmacol.* 145: 255, 1929.
99. Sumbal, J. J.: The Action of Pituitary Extracts, Acetyl-Choline and Histamine Upon the Coronary Arteries of the Tortoise, *Heart* 11: 285, 1924.
100. Dale, H. H., and Laidlaw, P. P.: The Physiological Action of β -iminazolyethylamine, *J. Physiol.* 41: 318, 1911.
101. Viotti, C.: Action de l'histamine sur le coeur et importance de l'atropine à cet égard, *Compt. rend. Soc. de biol.* 91: 1085, 1924.
102. Feldberg, W., and Schif, E.: Histamin, seine Pharmakologie und Bedeutung für die Humoralphysiologie, Berlin, 1930, Julius Springer.
103. Gold, H., Travell, J., and Modell, W.: The Effect of Theophylline With Ethylenediamine (Aminophylline) on the Course of Cardiac Infarction Following Experimental Coronary Occlusion, *AM. HEART J.* 14: 284, 1937.
104. Mahaim, I., and Rothberger, C. J.: Über die Wirkung von Euphyllin beim experimentellen Koronararterienversuchen, *Helvet. med. acta* 2: 687, 1936.
105. Laubry, C., Soulié, P., and Laubry, P.: Action de la Theophylline-Ethylenediamine sur la Circulation coronarienne, *Arch. d. mal du coeur* 30: 265, 1937.

106. Smith, F. M.: The Action of Nitrites on the Coronary Circulation, *Arch. Int. Med.* 28: 836, 1921.
107. Wiggers, C. J., and Greene, H. D.: The Ineffectiveness of Drugs Upon Collateral Flow After Experimental Coronary Occlusion in Dogs, *AM. HEART J.* 11: 527, 1936.
108. Douglas, A. H., Gelfand, B., and Shookhoff, A.: Production by Epinephrine of S-T Changes in the Electrocardiogram of the Cat, Similar to Those of Coronary Occlusion, *AM. HEART J.* 14: 211, 1937.
109. Richards, A. N.: A Note on the Combined Action of Camphor and Lack of Oxygen Upon the Isolated Mammalian Heart, With an Observation Upon the Isolated Mammalian Heart, With an Observation Upon the Direct Action of Lack of Oxygen Upon Blood Vessels, *J. Pharmacol. & Exper. Therap.* 6: 73, 1914.
110. Le Roy, G. V., and Speer, J. H.: A Comparison of the Coronary Vasodilator Activity of Certain Alkyl Xanthines, *J. Pharmacol & Exper. Therap.* 69: 45, 1940.
111. Blumgart, H. L., Riseman, J. E. F., Davis, D., and Berlin, D. D.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris. III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity (Case No. 5), *Arch. Int. Med.* 52: 165, 1933.

OCTYL NITRITE IN THE TREATMENT OF ANGINA PECTORIS

A. STONE FREEDBERG, M.D., ERWIN D. SPIEGL, M.D., AND
JOSEPH E. F. RISEMAN, M.D.
BOSTON, MASS.

OCTYL nitrite (2-ethyl-n-hexyl-1-nitrite) is a liquid nitrite of one of the higher alcohols which, because of its volatility, can be administered by inhalation. Krantz, Carr, and Forman,¹ who first prepared this substance, state that in laboratory animals it produces a fall in systemic blood pressure and an increase in the coronary blood flow; it dilates isolated coronary artery rings, and, in normal men, the inhalation of large doses (0.2 c.c. for one minute) produces a moderate fall in blood pressure, together with a moderate increase in heart rate. As a result of their studies, the investigators concluded, "Employing cotton impregnated with octyl nitrite, the compound lends itself to medication in an inhaler in the treatment of angina pectoris, asthma, and paroxysmal hypertension."

Although this drug has been available commercially for over a year, no objective studies of its efficacy in the treatment of patients are on record. The purpose of the present communication is to present objective measurements of the advantages and disadvantages of the "octrite inhaler" in the treatment of patients with angina pectoris.

The methods used in this objective evaluation were presented in a previous communication,² and include (1) The incidence and degree of beneficial effects, as measured by an increased ability to perform work under standardized conditions after administration of the drug in the dosage and manner usually employed in the treatment of angina pectoris, (2) adequate control studies, carried out in an identical fashion with inert preparations, (3) comparison of these results with the clinical response when the drug is used in daily life, (4) electrocardiographic studies on the same patients to confirm the results obtained by the other methods, (5) studies of the toxic effects and optimal dosage, and (6) comparison of these results with those obtained with nitroglycerin.

MATERIALS AND METHODS

The inhaler tubes* used in this study were made of brown glass approximately 3 inches in length, closed at each end by screw caps. Each tube was filled with cellulose pellets which were impregnated with a total of 2 c.c. of octyl nitrite. The

From the Medical Research Laboratories of the Beth Israel Hospital and the Department of Medicine, Harvard University, Boston.

Received for publication Feb. 21, 1941.

*Octrite inhalers were supplied by the Hynson, Westcott, and Dunning Co.

directions on the tube and on the package read as follows: "Octrile should be administered only under careful supervision of a physician. Inhaler should be applied to one nostril, the other being closed, until relief begins, according to the physician's directions. Remove both caps during use."

The subjects used in this study were twenty patients (seventeen men and three women) with angina pectoris of arteriosclerotic origin. They were observed in a special clinic once each week for a period of at least six months. The response to medication was studied for at least two months. Each test was performed on at least two different occasions, but only one test was performed at any one visit.

The optimum dosage and the untoward effects of octyl nitrite were ascertained by having each subject inhale deeply one, two, or three times on separate days, and observing both the untoward and desirable effects. The character and severity of the untoward effects were ascertained by observation and by the patient's description of his reactions. The clinical efficacy was measured immediately after the inhalation in the manner described below.

The efficacy of octyl nitrite in preventing attacks of angina pectoris on exertion was studied in twenty patients by comparing the amount of work which could be performed after inhalation of the optimum dose of the drug with that which could be done both when no medication was administered and also after inhalation of ethyl acetate from a similar tube. The work, in each instance, was done under constant, standardized conditions³ in a room kept at a temperature of 45 to 55° F., and consisted of repeatedly mounting and descending a two-step staircase until pain developed.

The efficacy of octyl nitrite was compared with that of nitroglycerin in nineteen of these patients. In these studies the amount of work which would be done after inhalation of octyl nitrite was compared with that which could be performed two minutes after placing a tablet of $\frac{1}{200}$ grain of nitroglycerin under the tongue.

Seventeen of these subjects were given octyl nitrite inhalers for home use. These patients were instructed to take the medication before any unusual physical or emotional strain. Once each week for eight to forty weeks these patients reported on the effect of the drug under these conditions.

The efficacy of octyl nitrite in shortening the duration of attacks of angina pectoris was ascertained in twenty patients by actual measurement in the laboratory, and also by clinical evaluation in eighteen of these subjects who tested the inhaler at home. In the laboratory the duration of attacks of angina pectoris induced by exertion was measured on several different days when no medication was taken. This was compared with the duration of attacks induced similarly on other days and treated immediately by the optimum number of inhalations of octyl nitrite. These results were also compared, in sixteen subjects, with the effect of placing nitroglycerin under the tongue immediately after inducing attacks by exertion.

After each of these tests in the laboratory, and also after each week of trial at home, the patient's evaluation of the efficacy of the drug in stopping attacks was recorded.

The duration of the effect of medication was studied by measuring on successive days the amount of work which could be performed at varying intervals after inhaling the optimum dose of the drug.

Electrocardiographic studies were carried out on nine patients according to a method previously described.^{2, 4} On at least two different occasions, electrodes were attached to both arms below the insertion of the deltoid muscles, and also to the precordium over the cardiac apex. A precordial lead (IVB) was taken with the patient standing at rest; the exercise test was then repeated with the electrodes in place and the electrocardiographic machine (but not the camera) running continuously. Immediately before the cessation of exercise, the camera was started and

a tracing was obtained for at least fifteen seconds after the onset of the attack; additional tracings were taken at one-minute intervals for five minutes after the cessation of pain.

On two subsequent occasions, octyl nitrite (two inhalations) was administered two minutes before the onset of exercise. Electrocardiograms were taken as noted above. No other medication was administered during the week prior to these electrocardiographic studies.

In the study of the electrocardiographic changes, ten consecutive complexes were measured and averaged; the P-R interval was taken as the isoelectric level.

RESULTS

The efficacy of octyl nitrite in preventing attacks of angina pectoris on exertion (Fig. 1).—Inhalation of the drug enabled fifteen of the twenty patients to do an appreciably greater amount of work before developing angina. Six of these patients were able to do at least 50 per cent more work than was possible when they were not taking the drug, and four of these six were able to exercise to the point of fatigue without developing pain.

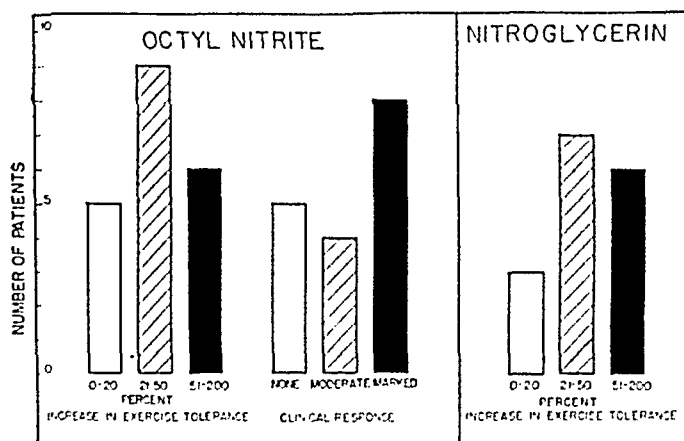


Fig. 1.—The efficacy of octyl nitrite in preventing attacks of angina pectoris on exertion, compared with the efficacy of nitroglycerin. The increase in exercise tolerance measures the frequency with which administration of drugs enabled patients to do more work under standardized conditions. The clinical response indicates the frequency with which the patients believed the drug to be of value when used in their daily life.

These results were similar to those obtained with nitroglycerin, except that the latter drug was somewhat more effective; it enabled six of nineteen patients to exercise to the point of fatigue without angina.

The five patients who were unable to do more work in the laboratory after taking the drug found the inhaler of no value in daily life. The remaining twelve of the seventeen patients who tested the drug at home reported that the inhaler was of definite value.

The efficacy of octyl nitrite in shortening the duration of attacks induced by exertion (Fig. 2) was best shown by the six patients whose attacks without medication were longer than one minute in duration.

Five of these patients showed a 17 to 64 per cent decrease in the duration of their attacks. These five patients also found that the drug was of value in shortening the duration of attacks experienced in daily life.

Only one of fourteen patients with attacks which were ordinarily less than forty-five seconds in duration showed an appreciable shortening of the attacks as a result of taking octyl nitrite. Another of this group showed an increase in the duration of pain following therapy. Similar results were obtained with nitroglycerin in eleven patients.

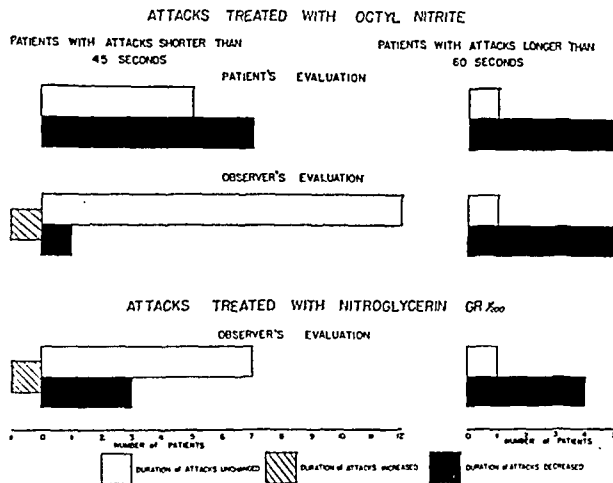


Fig. 2.—The comparative efficacy of octyl nitrite and nitroglycerin in decreasing the duration of attacks of angina pectoris. The patient's evaluation indicates the frequency with which patients believed the drug to be of value when used in daily life. The observer's evaluation indicates the frequency of changes in the duration of attacks as ascertained by actual measurement.

Eight of twelve patients who tested octyl nitrite at home believe that the drug was of definite value in shortening the duration of the attacks. None of these patients believed that the medication prolonged the duration of pain.

The optimum dosage and untoward effects of octyl nitrite were ascertained by studying fourteen patients (Fig. 3). The amount of the drug which was absorbed could not be measured with any degree of certainty, for it varied with the depth of inspiration; accordingly, the comparative effects of one, two, and three deep inhalations were studied. The optimum dose differed somewhat in different patients. In general, inhaling more than once increased the frequency and the severity of untoward reactions without increasing significantly the amount of work which could be performed. The optimum dosage for most patients was, therefore, one deep inhalation, or less.

The untoward effects of octyl nitrite became evident approximately thirty seconds after the inhalation of the drug. First, there was a definite flushing of the face, and the patient experienced a sense of

warmth, together with a fullness and pounding in the head. After one to four minutes this pounding increased and was accompanied by severe headache and dizziness. After the larger doses the patient frequently became pale, perspired freely, and complained of weakness and faintness which were so severe in some instances that the patient was forced to lie down. This marked reaction never occurred after one inhalation; it was seen in only one instance after two inhalations and was observed in four cases after three inhalations. One other patient, not included

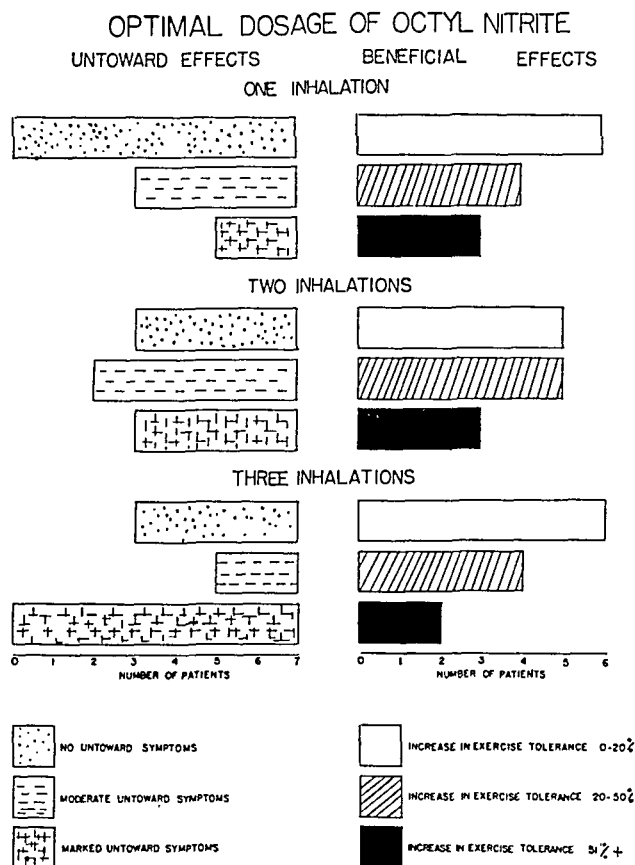


Fig. 3.—The optimal dosage of octyl nitrite.

in Fig. 3, took six inhalations in twenty-three seconds, was able to exercise for approximately one minute, and then collapsed. He complained of marked weakness, dizziness, and faintness. He appeared pale, perspired freely, and showed a marked fall in blood pressure, all of which persisted for approximately one-half hour. Three days later this patient was admitted to the hospital because of myocardial infarction, from which he recovered without complication. It is questionable whether this infarction was related in any way to the large dose of the drug which he absorbed; however, previous clinical reports^{5, 6} have pointed out the harmful effects which may be induced by overdoses of nitroglycerin. Furthermore, Blumgart, Schlesinger, and Zoll⁷

have shown that shock, with its attendant fall in blood pressure, may cause fresh coronary occlusion.

The duration of action of octyl nitrite was measured on three patients (Fig. 4). One subject was enabled to perform more work for at least twenty minutes after one inhalation, and another had an increased exercise tolerance for eight minutes. The third patient received no benefit from the drug. It is evident, therefore, that the duration of the action of octyl nitrite (like that of nitroglycerin) differs in different patients.

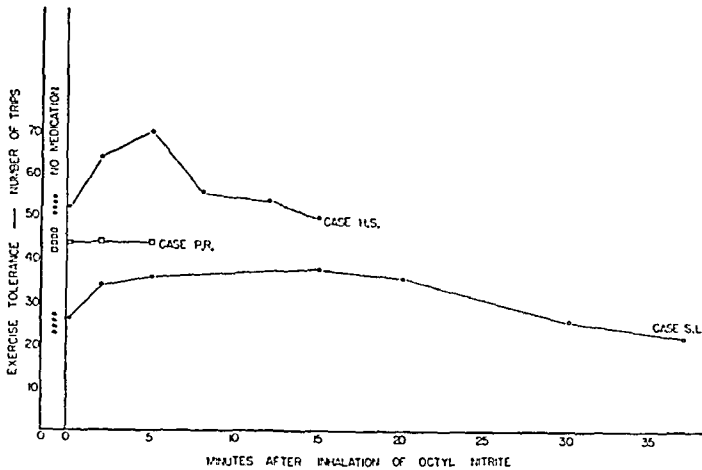


Fig. 4.—The duration of action of octyl nitrite.

TABLE I

OBJECTIVE EVIDENCE OF THE EFFICACY OF OCTYL NITRITE IN PATIENTS WITH ANGINA PECTORIS

PATIENT	NO MEDICATION**		OCTYL NITRITE			
			NO INCREASE IN WORK§		50% INCREASE IN WORK§	
	NO. OF TRIPS	S-T SEGMENT DEPRESSION* (MM.)	NO. OF TRIPS	S-T SEGMENT DEPRESSION* (MM.)	NO. OF TRIPS	S-T SEGMENT DEPRESSION* (MM.)
<i>Group I. S-T Changes Markedly Diminished Following Medication</i>						
H. Shl.	54	2.5	54†	0.5	81†	1.5
M. L.	40	1.8	40†	0.5	62†	0.5
H. Shr.	22	1.5	22†	0.0	40†	
S. L.	26	1.5	26†	0.2	42†	
R. C.	26	1.0	26†	0.0	42†	
<i>Group II. S-T Changes Moderately Diminished Following Medication</i>						
S. E.	27	2.7	27†	2.0		
L. W.	36	2.7	36†	1.8	54	1.4
<i>Group III. No S-T Changes Following Medication</i>						
P. R.	49	3.5	47	3.1		
B. A.	50	4.0	50	4.0		

*The average of the measurement of ten consecutive complexes.

†No attack of angina induced.

‡No pain on performing 50 per cent more work than was possible when no medication was taken.

§Increase in work as compared with the amount necessary to induce pain when no medication was given.

**Exercise was continued until attack was produced.

Electrocardiographic studies were made on nine patients (Table I). When no medication was given, the electrocardiograms immediately after the onset of pain induced by exercise showed a depression of the S-T

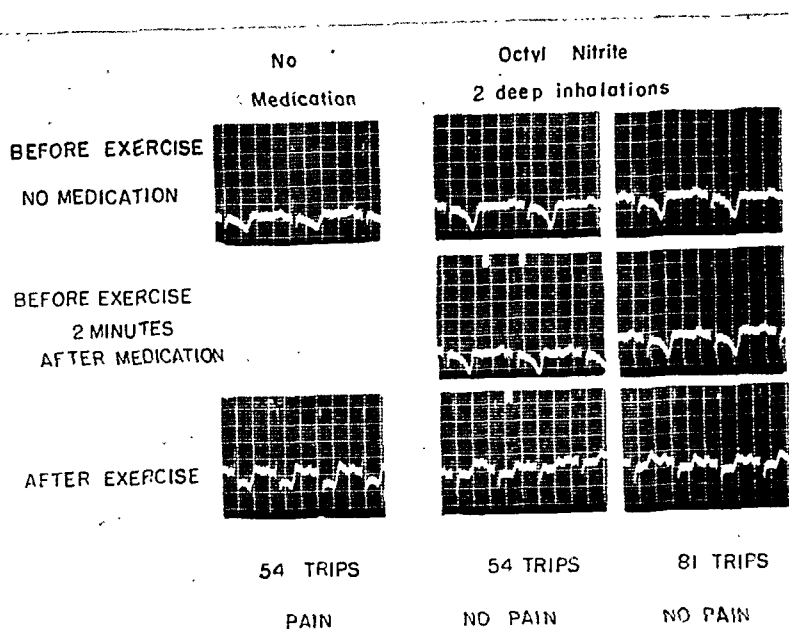


Fig. 5.—Marked response to octyl nitrite (Group I), as illustrated by results on patient H. Shl. When no medication was administered, fifty-four trips over the two-step staircase caused pain and a depression of the S-T segment averaging 2.5 mm. Two minutes after two inhalations of octyl nitrite the same amount of work caused no pain and a depression of the S-T segment of but 0.5 mm.; 50 per cent more work resulted in no pain and an average S-T segment depression of 1.5 mm.

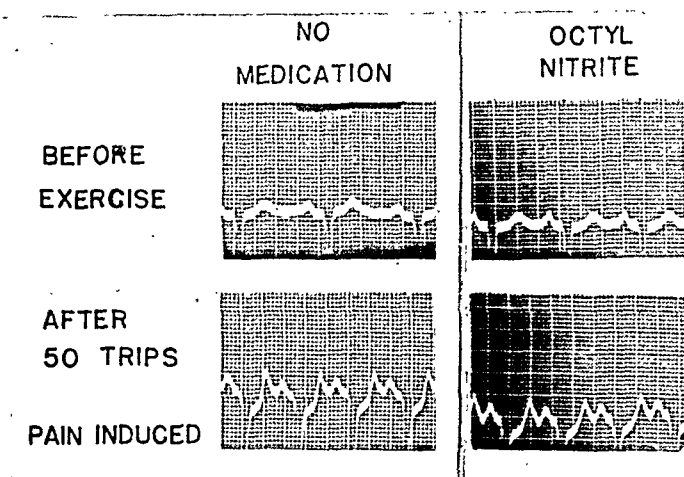


Fig. 6.—No response to octyl nitrite (Group III), as illustrated by results on patient B. A. When no medication was administered, fifty trips over the two-step staircase caused pain and an average depression of the initial portion of the S-T segment of 4.0 mm. The same results were obtained after inhalation of octyl nitrite.

segment of 1 to 4 mm., as compared to tracings taking at rest. This change was constant for each subject. Changes in the P, QRS, and T waves were variable and inconstant.

The inhalation of octyl nitrite with the patient standing at rest resulted in an average increase in heart rate of 11.6 beats per minute. Inhalation of the drug caused no constant change in the P, QRS, or T waves.

Five patients showed a marked change in the S-T segment as a response to the drug (Fig. 5). After exercise, the average depression of the S-T segment, when no medication was taken, was 1.7 mm., whereas, after medication, it was 0.2 mm. All five patients were able to do at least 50 per cent more work without developing pain. Two patients showed a moderate response to the drug; the average depression of the S-T segment after exercise when no medication was taken was 2.7 mm., and following the same stimulus after octyl nitrite was 1.9 mm. The remaining two patients showed no response to medication, either in an increased ability to work or in prevention of the S-T segment changes following exertion (Fig. 6).

The duration of efficacy and cost of the inhaler tube.—Four patients used the inhaler tube at home until it was no longer of any value in preventing or shortening the duration of attacks. The number of treatments before the tube became depleted was 44, 75, 120, and 180, respectively. Therefore, the cost of the medication was one to four cents per dose, or two to eight times that of nitroglycerin.

Observations on inhalation as a method of administering nitrites.—Although inhalation medication would seem to be a simple procedure, it was found that patients could not follow the directions on the label of the inhaler tube, and they obtained no benefit from the drug until the method of administration was demonstrated by the physician on at least one and frequently two or three different occasions.

Many difficulties were experienced with the commercial, glass inhaler tube. Breakage of the inhaler (which happened to at least one-third of the tubes which were used at home) was caused not only by dropping, but also by removal of the caps. The frequency of breakage not only added appreciably to the cost, but also deprived the patients of medication temporarily. The method of retaining the pledgets within the tube was faulty, for they would frequently fly into the nostril on deep inhalation. A further objection to the inhaler was the necessity for removing the two caps closing the ends; this frequently resulted in fumbling and loss of valuable seconds before the patient was able to take the medication. Although the patients found the odor of the drug unpleasant, it was not so objectionable as to prevent continuation of its use.

COMMENT

It is evident that octyl nitrite is definitely effective in the treatment of angina pectoris. This was shown objectively, not only by an increased ability to work after inhalation of the drug, but also by a definite decrease in the duration of the attacks in some cases. Further-

more, this drug, like others which are effective in angina pectoris,² prevents the development of the electrocardiographic changes which ordinarily occur on exertion in patients with angina.

Octyl nitrite is apparently similar in its action to nitroglycerin and amyl nitrite, and it has all of their advantages and disadvantages. It differs from nitroglycerin primarily in that, being volatile, it can be administered by inhalation; this attribute permits wide variation of the dosage but appears to be of little practical value. It is superior to nitroglycerin in that it is absorbed rapidly. This should make it more suitable than nitroglycerin for shortening the duration of attacks. In our experience, a rapidly soluble tablet of nitroglycerin requires twenty seconds for solution, and the effect of the drug becomes evident approximately one minute after placing it under the tongue.⁸ Octyl nitrite requires ten seconds, or less, for one inhalation, and the effect becomes evident within thirty seconds. Since attacks of angina pectoris are usually less than three minutes in duration,⁸ any method of treatment which makes the drug available more rapidly is of value. Octyl nitrite is more expensive than nitroglycerin, but less costly than amyl nitrite ampules. This is its main advantage over the latter drug.

These are definite drawbacks to the inhaler tube now on the market. The method of packaging makes it obvious that it is meant primarily for sale across the counter, and not solely on prescription. If the directions on the package are followed and the patient continues inhaling until relief begins, severe and even dangerous reactions may occur. One inhalation, only, should be used unless careful observation by the physician or the patient indicates that larger doses are safe and necessary. It is evident that the patient must be taught to use the inhaler correctly. It would seem advisable to modify the tube, not only to prevent breakage, but also to improve it mechanically so that the drug would be available more rapidly without the necessity of fumbling with the caps.

CONCLUSIONS

Octyl nitrite can be administered to patients with angina pectoris by the inhalation method. It is an effective means of preventing attacks on exertion and cutting short the duration of such attacks. Its action is similar to that of nitroglycerin and amyl nitrite, in both its beneficial and its untoward effects. It differs from nitroglycerin primarily in the mode of administration, which permits more rapid absorption but makes accurate dosage impossible. The commercial inhalers now available are not satisfactory. Dose for dose, octyl nitrite is much more costly than nitroglycerin, but less so than amyl nitrite.

REFERENCES

1. Krantz, J. C., Jr., Carr, C. J., and Forman, S. E.: Alkyl Nitrites. II. The Pharmacology of 2-Ethyl-N-Hexyl-Nitrite, *J. Pharmacol. & Exper. Therap.* 64: 302, 1938.

2. Freedberg, A. S., Riseman, J. E. F., and Spiegl, E. D.: Objective Evidence of the Efficacy of Medicinal Therapy in Angina Pectoris, *AM. HEART J.* 22: 494, 1941.
3. Riseman, J. E. F., and Stern, B.: A Standardized Exercise Tolerance Test for Patients With Angina Pectoris, *Am. J. M. Sc.* 188: 646, 1934.
4. Riseman, J. E. F., Waller, J. V., and Brown, M. G.: Electrocardiogram During Attacks of Angina Pectoris; Its Characteristics and Diagnostic Significance, *AM. HEART J.* 19: 683, 1940.
5. Proger, S. H., and Ayman, D.: Harmful Effects of Nitroglycerin With Special Reference to Coronary Thrombosis, *Am. J. M. Sc.* 184: 480, 1932.
6. Sprague, H. B., and White, P. D.: Nitroglycerin Collapse. A Potential Danger in Therapy, *M. Clin. North America* 16: 895, 1933.
7. Blumgart, H. L., Schlesinger, M. J., and Zoll, P. M.: The Occurrence of Multiple Fresh Coronary Occlusions With Antecedent Shock, *Arch. Int. Med.* 68: 181, 1941.
8. Riseman, J. E. F., and Brown, M. G.: The Duration of Attacks of Angina Pectoris on Exertion and the Effect of Nitroglycerin and Amyl Nitrite, *New England J. Med.* 217: 470, 1937.

THE EFFECT OF ABRASION OF THE SURFACE OF THE HEART UPON INTERCORONARY COMMUNICATIONS

EUGENE J. STANTON, M.D., PAUL SCHILDT, M.D., AND
CLAUDE S. BECK, M.D.
CLEVELAND, OHIO

EXPERIMENTS are recorded in which the surface of the heart was abraded by means of a metal burr, and the effect of this procedure upon the coronary arterial circulation was determined.

Abrasion of the surface of the heart was a component of the operation introduced by Beck¹ in the treatment of coronary artery sclerosis. The other components of this operation were the use of a foreign body, such as powdered beef bone, on the surface of the heart, and the grafting of vascularized tissues, such as fat, parietal pericardium, and skeletal muscle, upon the surface of the heart. The purpose of abrading the surface of the heart in this operation was to remove the epicardial barrier between the coronary arteries and the arteries of the grafted tissues. The purpose of using powdered beef bone was for the production of an inflammatory (foreign body) reaction on the surface of the heart. It was also pointed out in this paper that distribution of blood to every part of the myocardium was of vital importance. It was demonstrated experimentally that a small area of the heart muscle which had been made ischemic by the ligation of several peripheral branches of the coronary arteries became a trigger zone that set off ventricular fibrillation, whereas a much more marked reduction of total coronary flow was tolerated when the occlusion was placed centrally at the origin of the coronary arteries. It was also shown experimentally that complete occlusion of a major coronary artery was tolerated better if a vascular bed had been prepared by a previous operation. Ligation of the right coronary artery was followed by a recovery rate of 30 per cent in the normal heart and 66 per cent in the prepared heart.² This operation protected the heart in two ways: (1) It provided an extracoronary source of blood supply, and (2) it produced a more equitable distribution of blood between coronary arteries. Both extracoronary and intercoronary communications were demonstrated as a result of applying surgical procedures to the heart.³ "It seems quite possible," according to Mautz and Beck, "that the epicardial injury produced at the time

From the Laboratory of Surgical Research, Western Reserve University School of Medicine, and University Hospitals of Cleveland.

This work was aided by a grant from the John and Mary R. Markle Foundation.

Received for publication March 12, 1940.

of operation may lead to new intercoronary communications, when the injury is produced at the junction between obstructed and nonobstructed coronary arteries. As granulation tissue proliferates to repair an injury, new arterioles develop and in this way new arterial communications may form between two coronary arteries." Intercoronary communications which were produced by surgical methods were illustrated in Fig. 8 of that publication. However, studies have not been made to ascertain the relative importance of these factors. The experiments reported here concern intercoronary communications without the presence of extracoronary communications. This publication deals with the effect of abrading or scraping off the epicardium. A later publication will concern the effect of powdered beef bone and other agents upon the development of intercoronary communications.

EXPERIMENTS

A. The Coronary Arteries in the Normal Heart and in the Abraded Heart

In ten experiments on dogs the entire surface of the heart was thoroughly abraded. Frequently the epicardium came away in sheets of 1 sq. cm. or larger. The experiment was terminated one week to three months later. The circumflex ramus of the left coronary artery and the right coronary artery were cannulated, washed with a little physiologic saline, and injected with a barium sulfate gelatin mixture under a pressure of 200 mm. of mercury.⁴ This injection mass entered small arterioles, but did not fill capillaries and arteriololuminal vessels. These two arteries in normal hearts were similarly injected for comparison. Roentgenograms of the specimens were taken (Figs. 1 and 2). The amount of injection mass that passed over into the descending ramus of the left coronary artery was variable in each individual heart. The amount that did pass over was assumed to be an indication of the size and number of intercoronary communications between the beds that were cannulated (circumflex ramus of left coronary artery and right coronary artery) and the noncannulated bed (descending ramus of left coronary artery). Analysis of these results is shown in Fig. 3. According to this comparative classification, a good injection was obtained in five abraded hearts and in no normal heart; an intermediate injection was obtained in two normal hearts and in one abraded heart; a slight injection was observed in four normal hearts and in one abraded heart; and no injection occurred in four normal hearts and in three abraded hearts. It should be pointed out that a considerable variation existed in the communications between one coronary artery and another. A rare specimen was found among normal hearts in which these communications were numerous and large enough to transmit blood, whereas other specimens failed to show any communications.³ It is obvious from this study that the abraded hearts as a group are different from the normal



Fig. 1.—Roentgenograms of the normal hearts with barium sulfate gelatin mixture injected into the ramus circumflexus of the left coronary artery and the right coronary artery. Note the injection of the descending ramus of the left coronary artery in *a*, *b*, *c*, *d*, and *e*, as indicated by arrows, and the absence of injection of this artery in the other specimens.

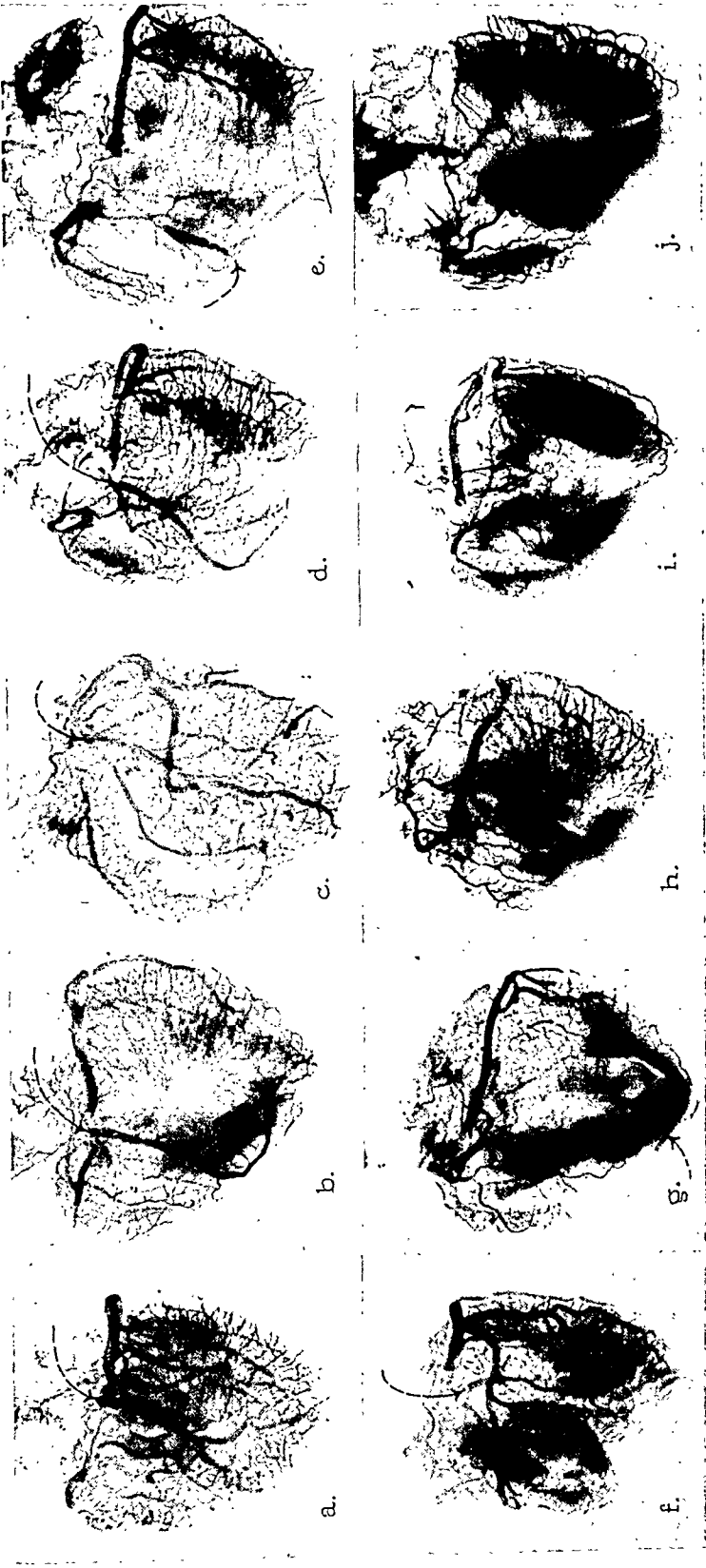


Fig. 2.—Roentgenograms of ten hearts, the surfaces of which were abraded one week to three months before injection. Specimens were injected as in Fig. 1. Note the injection of the descending ramus of the left coronary artery in *a*, *b*, *c*, *d*, *e*, *f*, and *g*, as indicated by arrows, and the absence of injection of this artery in the other specimens.

hearts as a group. The difference between the two groups is better injection of the descending ramus in the abraded specimens. Indeed, it seems that one might be able to select the hearts that might survive ligation of the descending ramus of the left coronary artery at its origin in one step and those that might not survive ligation of this artery. We should expect survival to take place in *a*, *b*, *c*, *d*, *e*, and *f* of the abraded group (Fig. 2), and in *a*, *b*, and questionably in *c* of the nonabraded group (Fig. 1). This estimate can be compared with results obtained in 110 experiments in which this artery was ligated.

Communications between Descending Ramus and Other Coronary Arteries.			
Good	Intermediate	Slight	Absent
○	● ○	● ○	● ○
○	●	●	● ○
○		●	● ○
○		●	●
○			

●=Normal hearts

○=1 week to 3 months after surface of
heart was abraded

Fig. 3.—Ten normal and ten abraded hearts injected with barium sulfate gelatin into circumflex branch of left coronary artery and into right coronary artery. The specimens are classified according to the amount of the injection mass found in the descending ramus of the left coronary artery.

B. Ligation of the Descending Ramus of the Left Coronary Artery at Its Origin in Normal Hearts and in Abraded Hearts

Mortality.—Ether anesthesia was used. Artificial respiration was carried out by means of an intratracheal tube. A surgical dissection of the descending ramus of the left coronary artery at its origin was made. The common left artery was exposed at its bifurcation. Two ligatures were placed on the descending ramus, and the artery was transected between ligatures. In this way only can we be certain that ligation of the artery is proximal to its highest branches. Ligation at lower levels has introduced a variable factor that is not uncommonly referred to in the literature. This artery was ligated in five groups of ten dogs each. In one group two operations were performed because it was suggested that two exposures of the heart might make some difference in the result. In this group the dissection of the artery was carried out, and a piece of silk was passed beneath the vessel; no obstruction to the vessel was produced. Two weeks later the artery was doubly ligated and transected. The result was that four dogs lived and six died. The total mortality is shown in Table I. Recovery occurred in fifteen experiments, or 30 per cent, and death occurred in thirty-five experiments, or 70 per cent. The variations in the five groups of ten each ranged from

recovery of one to recovery of five. We feel that this difference must be due to variations in individual hearts with regard to the number and size of intercoronary communications and the relative size and importance of the three major arteries themselves.

TABLE I A
LIGATION OF DESCENDING RAMUS OF LEFT CORONARY ARTERY

DOGS	LIVING	DEAD
10	3	7
10	1	9
10	4	6
10	2	8
10	5	5
Total 50	15 (30%)	35 (70%)

TABLE I B
ABRASION OF EPICARDIUM FOLLOWED BY LIGATION OF ARTERY

DOGS	INTERVAL (WEEK)	LIVING	DEAD
10	Same operation	4	6
10	1	6 (60%)	4
20	2	14 (70%)	6
20	3	11 (55%)	9
Total 50		31 (62%)	19 (38%)

Results of 110 experiments, in fifty of which the descending ramus of the left coronary was ligated and cut at its origin, and in sixty of which the surface of the heart was abraded before ligation and section of the same artery.

In ten experiments the surface of the heart was abraded, and after this was done, and at the same operation, the descending ramus of the left coronary artery at its origin was doubly ligated and transected as in the control experiments. The result in this group was that four lived and six died. This result was the same as that in one of the control groups, and indicates that no obvious benefit was obtained by abrasion when the two procedures were done simultaneously.

In one group of ten and two groups of twenty experiments each, abrasion of the heart was followed by ligation and section of the artery, as in the control groups, at intervals of one, two, and three weeks, respectively, between abrasion and ligation. The results of these experiments, in order, were that six lived and four died; fourteen lived and six died; and eleven lived and nine died. The total result was thirty-one survivals, or 62 per cent, and nineteen fatalities, or 38 per cent (Table I). All animals were kept for periods of at least two months after ligation of the artery in order to obtain these statistics. According to these results, the mortality after ligation of the descending ramus of the left coronary artery at its origin, in one step, was reduced from 70 per cent in fifty normal hearts to 38 per cent in fifty hearts in which the surface of the heart had been abraded one to three weeks before the artery was ligated.



Fig. 4.—The specimens were arranged into four groups according to the size of the infarct. *a*, No infarct; *b*, small infarct; *c*, intermediate infarct; and *d*, large infarct. This is key for Fig. 5.

Infarcts.—At any time after a two-month period the experiment was terminated and the specimen examined. The circumflex branch of the left coronary artery and the right coronary artery were cannulated and injected as in the control groups. The descending ramus of the left coronary artery was not injected. The specimens were chilled after injection to fix the injection mass, and the specimen was preserved in formalin. After fixation, roentgenograms of the specimens were taken and then four or five transverse sections were made across the heart. The infarcts were classified, according to size, as none, small, intermediate, and large. Examples from this classification are shown in Fig. 4. With this illustration as a key, the specimens were arranged in groups, as shown in Fig. 5. In two specimens no infarct was found. Both of these hearts had been abraded before the artery was ligated. A small infarct was found in four control specimens and in seven abraded specimens. An intermediate infarct was found in four control specimens and in ten abraded specimens. A large infarct was found in seven control specimens and in twelve abraded specimens.

Surviving Ligation Descending Ramus Left Coronary Artery			
Size of Infarct			
None	Small	Intermediate	Large
○ ○	● ○ ● ○ ● ○ ● ○ ○ ○ ○	● ○ ● ○ ● ○ ● ○ ○ ○ ⊕ ⊕ ⊕ ⊕ ⊕ ⊕	● ⊕ ● ⊕ ● ⊕ ● ⊕ ● ⊕ ● ⊕ ● ⊕ ⊕ ⊕ ⊕ ⊕ ⊕ ⊕
● = Survivals from 50 normal hearts.			
○ } = Survivals from 50 ⊕ } hearts abraded 1 week to 3 weeks before ligation of artery.			
⊕ = Survival due to abrasion, on proportional basis.			

Fig. 5.—Results with fifty abraded and fifty normal hearts in which the descending ramus of the left coronary artery was ligated in one step at its origin. The group in which abrasion and ligation were done at the same operation is not included.

Two conclusions are obvious in the analysis of these results. One is that abrasion tends to reduce the size of the infarct, making it possible to ligate the descending ramus of the left coronary artery at its origin without the formation of an infarct. This, in our experience, never occurred in a normal, unabraded heart. The other conclusion is that there are more abraded specimens than control specimens in every group—small, intermediate, and large. On a percentage basis, it appears that the lives of sixteen of fifty dogs were saved by abrasion of the surface of the heart before the artery was ligated.

Injected Specimens.—On examination of the specimens it was found that many of the hearts that survived ligation of this artery, whether of the control group or of the abraded group, showed well-developed communications between the ligated artery and the other two patent arteries (Fig. 6). Good communications were present regardless of the size of the infarct. It would appear from these results that, if recovery followed ligation of the descending ramus of the left coronary artery, the entire vascular bed frequently became one common bed. The cause for the development of a common arterial bed is the existence of a pressure differential in the open arterial tree, as compared to the closed

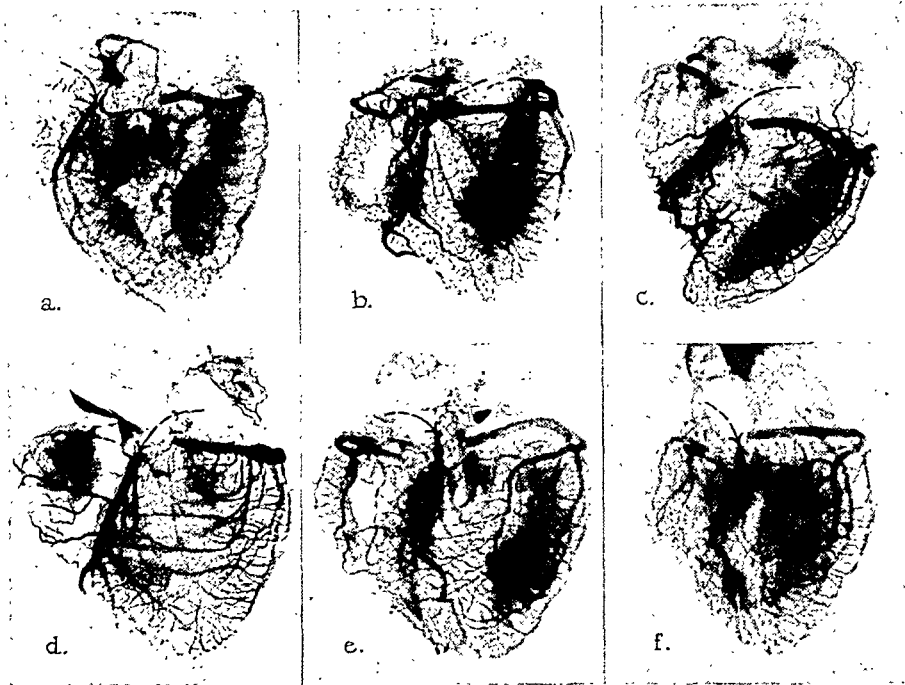


Fig. 6.—Roentgenograms of hearts that survived ligation of the descending ramus of the left coronary artery at its origin. The right coronary artery and the circumflex branch of the left coronary artery were injected. The descending ramus filled well through intercoronary communications, which became progressively larger after ligation, regardless of the size of the infarct. A common coronary bed was produced by the ligation; this is a favorable condition in the presence of progressive coronary artery sclerosis. Arrow points to the ligated descending ramus.

arterial tree. It is conceivable that the small anatomic communications that normally extend into adjacent vascular beds are opened up by this pressure gradient.⁵ These communications undergo progressive enlargement until they carry a considerable quantity of blood. This is a favorable anatomic and physiologic condition, and it should offer a degree of protection against further coronary occlusion. In a study of human hearts with coronary artery disease, Blumgart, Schlesinger, and Zoll⁶ found that, in the majority, two of the three major arteries were occluded. After the subject survived occlusion of one major artery and after a common coronary bed developed, it would appear that this com-

mon circulatory tree was adequate to carry on until another major artery was occluded. Were it not for the development of a common bed, one would expect catastrophe earlier in the course of the occlusive process.

SUMMARY AND CONCLUSIONS

We have demonstrated that intercoronary communications can be produced by surgical methods. Abrasion of the surface of the heart was the surgical method used in these experiments. This surgical procedure was effective in opening intercoronary communications. It reduced the death rate from 70 per cent to 38 per cent after ligation of one of the three major coronary arteries. In terms of recovery, there was an increase from 30 per cent to 62 per cent. With respect to irreparable damage to the heart muscle after ligation of a major coronary artery, we can say that abrasion exercises a favorable effect. The infarct caused by acute arterial occlusion is smaller or, indeed, can be altogether prevented from forming in hearts that have been abraded. We can also say that in 32 per cent of the animals the heartbeat was maintained by virtue of the intercoronary communications that developed after the surface of the heart had been abraded. In these dogs infarcts developed; large infarcts developed in many of them. The coronary circulation in these dogs under normal conditions was such that the heart could not have tolerated occlusion of the artery if the circulation had not been aided by the effect of abrasion. After abrasion, the circulation in these hearts was good enough to withstand ligation.

We have shown that, if the heart survives ligation of a major artery, the arterial bed usually becomes a common bed through the medium of intercoronary communications. Coronary occlusion is an effective stimulus to the development of intercoronary channels.

REFERENCES

1. Beck, C. S.: The Development of a New Blood Supply to the Heart by Operation, *Ann. Surg.* 102: 801, 1935.
2. Beck, C. S.: Further Data on the Establishment of a New Blood Supply to the Heart by Operation, *J. Thoracic Surg.* 5: 604, 1936.
3. Mautz, F. R., and Beck, C. S.: The Augmentation of Collateral Coronary Circulation by Operation, *J. Thoracic Surg.* 7: 113, 1937.
4. Gross, Louis: The Blood Supply to the Heart, New York, 1921, Paul B. Hoeber, Inc.
5. Wiggers, C. J.: The Physiology of the Coronary Circulation. Diseases of the Coronary Arteries and Cardiac Pain, edited by Robert L. Levy, New York, 1936, The Macmillan Co., Chap. II.
6. Blumgart, H. L., Schlesinger, M. J., and Zoll, P. M.: Angina Pectoris, Coronary Failure and Acute Myocardial Infarction, *J. A. M. A.* 116: 91, 1941.

THE CORONARY OPERATION

CLAUDE S. BECK, M.D.

CLEVELAND, OHIO

THE original idea of revascularization of the myocardium occurred to me in 1931. During the years which have intervened since then, my associates and I have carried out several thousand experiments on dogs' hearts in a study of this and related problems. I have always felt that the surgeon was obliged to prove or demonstrate his point in the laboratory before he tried to apply his idea by operating on the human heart. In several instances, surgeons have gone ahead with operations on the human heart in the hope that the patient would be helped by the operation and that the science would come later. I am critical of this short cut. It is an easy road to take, but it is dangerous and it may be futile. Interest should center first and foremost in experimental demonstration. If experimental demonstration is reasonably acceptable, then we can go to the patient. What we have done on this subject, we have done the hard way. It has been slow and difficult, but we have not applied any idea to the patient that was not investigated first in the laboratory.

I shall refer briefly to some of the facts established by experiment. We established extracoronary communications in grafts. These channels were demonstrated in cleared specimens and were large enough to be seen without magnification. We have not ascertained the direction of flow in these channels, nor have we measured the amount of flow through them. From the scientific point of view it matters little what tissues are used for grafting. The important point is the demonstration of blood vessels. This, I might add, is not a trifling accomplishment if one insists upon the demonstration of blood vessels large enough to be seen without magnification. I feel that, if the graft is going to furnish any significant quantity of blood to the heart, the anastomoses should be large enough to be seen without a microscope. For that reason we gave up the use of watery solutions of dyes for injection purposes, and, in later years, injected our specimens with a mixture of barium sulfate and gelatin. Blood vessels demonstrated by the injection of aqueous solutions may be so small that they may not carry blood. In this respect they are anatomic, but not functional. Vessels injected with the mixture of barium are 40 to 50 micra, or larger, in diameter, and can carry blood. We used many different structures for grafts—parietal pericardium, mediastinal fat, skeletal muscle from the chest wall, lung, omentum brought

From the Department of Surgery, Western Reserve University School of Medicine and University Hospitals of Cleveland.

Received for publication March 12, 1941.

up through the diaphragm, spleen, stomach, and bowel. We also used island grafts of internal mammary artery and triangularis sterni muscle. We were the first to use omentum experimentally, but this is not an important consideration. The important point was to produce as many anastomoses as possible, and to make them as large as possible, regardless of the tissue used.

Doctors Tichy, Bright, Mautz, Thornton, Phelps, and Stanton assisted in the study of these problems. We had the belief early in the work that occlusion of the coronary arteries was helpful in the development of anastomoses. To produce occlusion of a coronary artery progressively over a period of time was a problem in itself. Finally and recently, a clamp was devised that could close an artery in four to six weeks by virtue of osmotic pressure. It was shown that, if one of the three major coronary arteries was occluded in stages at successive operations, an infarct did not form. This was an original experimental demonstration. Bright completely occluded the descending ramus of the left coronary artery in stages, and he and Tennant, in Dr. Wiggers' laboratory, showed that the myocardium supplied by this artery maintained its function. It contracted, and did not dilate, as did the myocardium after arterial ligation in the normal, unprepared heart. It was also shown in a few specimens that practically all three major coronary arteries (except the septal artery) could be occluded if the heart had been prepared before the arteries were occluded. We believed that the epicardium was a barrier to the development of extracoronary vessels, and we removed it by various destructive chemical agents, or by a metal burr. We conducted experiments with many foreign bodies on the surface of the heart for the purpose of obtaining an inflammatory reaction. Many of these substances were dangerous, and could not be used on human patients, such as tincture of iodine, Dakin's solution, ether, iron filings, etc. We used powdered beef bone because it produced a mild, foreign-body type of inflammation over a long period of time. Communications were demonstrated between the coronary arteries themselves, and between coronary arteries and arteries of grafted tissues. It was also possible to demonstrate anastomoses extending into the fat at the base of the heart. Anatomic communications normally exist in this fat. They do not carry blood under normal conditions. These channels can be enlarged by surgical methods, and perhaps they can be made to carry blood.

I should like to discuss a point that was learned early in the course of the work which I believe is of importance. It has been published in one of our surgical journals (*Annals of Surgery* 102: 801, 1935), but I have not seen it discussed in any of the medical contributions on coronary disease.

When we began to produce coronary obstruction, we did not know whether we should ligate the arteries distally or ligate them close to

their origin from the aorta. A surgical dissection of these vessels at the aorta appeared to present technical difficulties at the time, and we therefore selected peripheral ligation. Four or five small arteries were ligated over the left ventricle, as shown in Fig. 1*b*. I believe we did this experiment about two dozen times before we finally concluded that this was always a fatal procedure. The ventricles went into fibrillation. Then we went up higher on the arteries and placed silver bands on each artery, as in Fig. 1*a*, reducing the cross section of each artery about one-third.

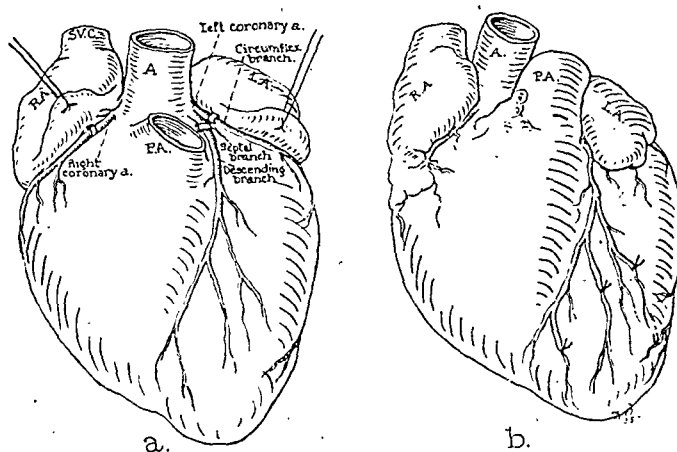


Fig. 1.—Two types of operations are shown: *a* shows the usual sites where silver bands were applied to the coronary arteries. A reduction of 30 to 50 per cent in the cross sectional area of these three arteries was compatible with life. *b* shows another type of experiment. Four or five peripheral branches of the coronary arteries over the apex of the heart were ligated. This experiment was always fatal. In *a* the reduction in total coronary blood flow was considerably greater than in *b*. The heart cannot tolerate ischemia of severe degree, even when the area of ischemia is small. The collateral bed produced by operation can transport blood to such ischemic areas.

The heart could tolerate this degree of obstruction. When one experiment is compared with the other, it would appear that we were dealing with generalized anoxemia in *a*, and localized, but severe, anoxemia of a small part of the myocardium in *b*. I believe the entire coronary circulation was reduced to a greater extent in *a* than it was in *b*, yet recovery took place in *a* and ventricular fibrillation took place in *b*. This experiment made us pay attention to localized anoxemia, and it convinced us that localized anoxemia in the heart was like a trigger that could set off ventricular fibrillation. I believe that the concept of a trigger zone is appropriate, because it implies potential danger to a mechanism that is working smoothly, and, as the clinician well knows, its presence may be entirely unsuspected. We could appreciate this very clearly in the laboratory, and it started us to think about the distribution of blood to the myocardium. We recognized the importance of an equal distribution of blood to all parts of the myocardium, and we came to believe that we could improve distribution of blood by surgical methods. This was accomplished by bringing in blood from the outside through grafts, and also by opening intercoronary channels by producing an inflammatory reaction on the surface of the heart. Both of these developments are important.

Intercoronary communications can be produced in two ways. One is by gradual, progressive occlusion of a major artery. The other is by the production of an inflammatory reaction on the surface of the heart. Both of these demonstrations are original contributions from our laboratory. Abrasion of the surface of the heart is effective in opening intercoronary communications. Foreign bodies and chemical agents are also effective. Each of these methods can function in a mutually complementary manner, as I shall try to show. We can readily understand how a trigger zone develops in the myocardium because of arterial disease. Anything in the way of improved distribution in the early stage of the disease will delay or remove the threat of ventricular fibrillation. The opening or the development of new, intercoronary communications in the early stages of the disease should be able to accomplish this. The intercoronary communications develop as the occlusive process develops. It is obvious that catastrophe can be delayed by the presence of a common coronary bed. It is reasonable to believe that surgical methods are effective in the production of a common bed.

The coronary problem was studied over a three-year period before any application to the human heart was attempted. Dr. Harold Feil selected thirty patients for operation. They were to constitute a study group. The operation was not looked upon as a matter of therapy. The first operation was performed on Feb. 13, 1935; the last in this study group was performed on April 19, 1938.

The first requirement in the selection of the patient for operation was that he should be severely crippled by the disease. We did not accept anyone who could get along moderately well with bed rest and drugs, and no one who could hold down any kind of job was taken. We did not desire to take patients who had circulatory failure. However, one patient had severe edema and dyspnea at the time of operation. The point that I should like to make is that we did not feel justified in taking patients who seemed to have a chance to keep on living, and each patient felt that he was facing imminent catastrophe without operation.

A follow-up report of results was presented to the American Association for Thoracic Surgery, in 1940, by Dr. Feil, and was published in the journal of that association (10: 529, 1941). As I look at this part of the work at its present stage of development, I can see that certain considerations are of greater importance than others. I would not give a place of first importance to such considerations as selection of patients, details of operation, whether omentum or something else should be used, and mortality. I believe the most important question is this: Has operation helped anyone in the group? The answer to this question determines whether or not medical methods of treatment of coronary disease will prevail without exception, or whether operations will be performed upon some of these patients. The second important question is this: What is

the best result from operation in the group? The answer to this question provides a measurement of the best that operation can give—a standard of attainment, so to speak. The third question is: What is the explanation of the clinical improvement? The answer to this will tend to keep the operative technique on a scientific basis. If surgery finds a place in the treatment of coronary disease, the technique will undergo changes. Someone will advocate the use of a foreign body only, without grafts, as I did in the thirteenth patient of our series five years ago. This patient had circulatory failure, and it appeared that he would not stand much in the way of an operation. We opened the pericardium and introduced powdered beef bone to obtain an inflammatory (foreign body) reaction on the surface of the heart without using any grafts. Someone will conceive the idea of injecting a chemical agent, such as sodium morrhuate, sodium ricinoleate (or croton oil, which should never be used) into the pericardial cavity without exposing the heart and without operation. I should like to repeat here that all procedures should be tested in the laboratory before they are applied to patients. Many substances cannot be tolerated and will cause death.

In answer to the first question, I can say that, with exceptions, the operation is beneficial. Ten of the thirty patients died during the immediate postoperative period. All of these patients had severe coronary disease, as shown by necropsy examination. I do not believe that the operation in itself need be more severe or shocking than any ordinary operation. Of the twenty patients who were discharged from the hospital, sixteen are still living and four are dead. Every one of the sixteen has been improved, and twelve of them have what Dr. Feil calls a good result.

It is a pleasure for me to answer the second question. The degree of benefit has been great. Indeed, it is almost incredible. The first patient in the series was operated upon six years ago. Four months after operation he got a job as a gardener. For the past four years he has worked as a farm hand. He has no symptoms. The second of those now living is a surgeon. He was operated upon six years ago. He believes the operation saved his life. He also believes that the operation should be applied as a matter of therapy. The list of patients includes several salesmen, several machinists, a factory superintendent, a school teacher, a painter, a cook, a clerk, a coal miner, a waiter, and a moulder. Not all are back at work, but many of them are, and every one of them states that he is better than he was before the operation. I have asked Dr. Feil whether results like this could occur in a group of similar patients who were not operated upon. He states that it is unusual for a patient, after he has had a coronary thrombosis, to recover to such an extent that he can resume manual labor and be able to work for a period

of several years. Although this might occur in unusual instances, a group experience such as this, he states, does not occur.

I believe the scientific explanation for the improvement in our group of patients can be given in a fairly reasonable manner. We have been fearful to accept the beneficial result obtained in the patients until we demonstrated that abrasion of the heart was a more important factor than we appreciated in the past. Up to this time the clinical result was better than our laboratory demonstrations could explain satisfactorily. We could not understand why many of the patients stated that they felt better as early as one week after the operation. The earliest that we could demonstrate injection across the grafts, using watery solution of dye, was two to three weeks, and we did not believe that the circulation through the grafts could provide such early improvement. I can accept the explanation now that intercoronary communications were opened by the abrasion, and that this explains the early improvement which was noted so frequently. Some of the patients showed continuing improvement after a two-year period. We do not know what will happen to extracoronary communications in the course of years, whether they will increase or diminish in size. The relative importance of intercoronary and extracoronary communications remains to be ascertained. In the best of the three human hearts that we examined, we found that the mixture of barium sulfate and gelatin which was injected into the coronary arteries escaped through the grafts. The transfer was through about ten or twelve anastomoses that could be seen in the cleared specimen without magnification. Intercoronary channels were also present, and these could have been developed by the operation or by the progressive narrowing of the coronary arteries higher up. Additional information on this will be obtained in the future.

Up to the present time I have considered the work as an experimental study, and I have advised against accepting it as a matter of therapy. The experiments by Stanton, Schildt, and myself are encouraging, as are also the experiments by Heinbecker and Barton, of St. Louis. It appears to me that we should continue to regard the work as an experimental study, and not as a matter of therapy. I do not believe that the operation is ready for surgeons to take up generally. However, I should like to solicit the help of the American Heart Association in selecting a number of patients who are willing to have the operation done, so that a preliminary appraisal of results can be made by people other than ourselves. I believe that it would be advisable to carry out the operation on 100 patients as a preliminary study, before deciding the question of therapy. I should be pleased to do these operations because the technical aspects of the operation should be controlled. Cooperation in this preliminary study is needed.

SYMPATHECTOMY AND EXPERIMENTAL OCCLUSION OF A CORONARY ARTERY

ARNALDO YODICE,* M.D.
BUENOS AIRES, ARGENTINA

THE purpose of this paper is to record experiments in which the sympathetic nerves to the heart were removed and a major coronary artery was ligated. Leriche, Herrmann, and Fontaine^{1, 2} maintained that removal of the sympathetic nervous system protected the heart when the descending ramus of the left coronary artery was ligated. This conclusion was based upon four experiments. Cox and Robertson³ asserted that the mortality was reduced from 50 to 10 per cent after ligation of this artery in the normal heart if the stellate ganglia had been removed before the ligation. They also stated that the infarct caused by ligation of the artery was smaller if the stellate ganglia were removed before ligation. Mendlowitz, Schauer, and Gross⁴ pointed out that the heart rate became slower after removal of the sympathetic chain, but this bradycardia was only temporary. Bilateral sympathectomy produced fatal heart block in a few of their experiments. Schauer, Gross, and Blum⁵ reported measurements of cardiac output, circulation time, and arterial pressures in animals after ligation of the descending ramus of the left coronary artery. In some experiments the stellate ganglia were removed before the artery was ligated. In both types of experiments there were a fall in cardiac output, a delay in the circulation time, and a fall in blood pressure. Sympathectomy reduced the incidence of ventricular fibrillation and the mortality rate after arterial ligation. The size of the infarct was the same in both types of experiments.

My interest in repeating these experiments was to ascertain whether the effect of sympathectomy was sufficiently beneficial to apply the procedure in the treatment of coronary sclerosis.

EXPERIMENTS

The stellate ganglia and the sympathetic chain down to the eighth, ninth, or tenth rib were removed on both sides. The left coronary artery was dissected at its bifurcation into the ramus circumflexus and the ramus descendens. The latter was isolated, doubly ligated, and cut. This high level for ligation of the artery was selected in each experiment. The operations were carried out under ether anesthesia.

In one series of experiments this procedure on the sympathetic nervous system was completed and was followed by ligation of the artery at the

Aided by a Grant from the Josiah Macy, Jr., Foundation.

Received for publication March 12, 1941.

Docente Libre de Patología Quirúrgica y de Clínica Quirúrgica cirujano y Jefe de Clínica del Hospital Ramos Mejía, Buenos Aires.

*Visiting Fellow, University Hospitals and Laboratory of Surgical Research, Western Reserve University, Cleveland.

same operation. In the other series of experiments, an interval of eleven to twenty-five days (average, about seventeen days) elapsed between removal of the sympathetic system and ligation of the artery. The results of these experiments are given in Tables I and II.

TABLE I

DOG	INTERVAL BETWEEN SYMPATHECTOMY AND LIGATION OF CORONARY ARTERY (DAYS)	RECOVERED	DIED
1	11	Killed after 3 mo.	1 day
2	17		1 day
3	17		2 days
4	16		1 day
5	25		4 hours
6	17	Killed after 53 days	7 days*
7	16		1 day
8	19		1 day
9	17		1 day
10	20		5 min.
11	20	Killed after 48 days	2 hours
12	19		12 min.
13	17		3 days*
14	17		30 min.
15	17		
16	17		

Bilateral sympathectomy and ligation of descending ramus of the left coronary artery at its origin were done in two operations.

*Two animals had pneumonia (Experiments 7 and 15).

TABLE II

DOG	RECOVERED	DIED
1		5 min.
2		1 day
3		6 days*
4		7 days*
5	Killed after 23 days	
6	Killed after 23 days	
7		2 days*
8		10 min.
9	Killed after 44 days	
10	Killed after 44 days	
11	Killed after 43 days	
12		1 day
13		2 days*
14		1 day
15		4 days*
16		10 min.
17		1 day
18	Killed after 38 days	

Bilateral sympathectomy and ligation of descending ramus of left coronary artery at its origin were done at the same operation.

*Pneumonia was found in Experiments 3, 4, 7, 13, and 15.

The control experiments consisted of ligation of the artery only. This group of experiments was done by Beck and Mako,⁶ in this laboratory (Table III).

In ten experiments, procaine was applied to the surface of the heart before and after the descending ramus of the left coronary artery was

ligated. Two cubic centimeters of a 5 per cent solution of procaine, when applied to the epicardium, produced slowing of the heart rate and reduced the responses of the heart to mechanical, electrical, and chemical stimuli. This drug was applied both before and after ligation of the artery. In a series of ten experiments, five animals survived ligation and five died. In two experiments, ventricular fibrillation occurred a few minutes after ligation of the artery; two animals died on the first day, and one died on the second day after ligation. The application of procaine to the surface of the heart did not prevent ventricular fibrillation after the artery was ligated. The fact that five of ten dogs survived suggests that the drug may have a beneficial effect, but, if so, it is slight.

TABLE III

DOG	LIVING	DEAD
10	1	9
10	2	8
10	3	7
Total 30	6—20%	24

Control experiments in which the descending ramus of the left coronary artery at its origin was ligated. Analysis of deaths shows that seven died 5 to 30 minutes, fifteen, 2 to 18 hours, one, 15 days, and one, 18 days, following ligation.

The size of the heart was ascertained before and after operation by means of standardized roentgenograms. These were taken with a constant target-film distance. According to these measurements, the size of the heart was the same before and after sympathectomy.

The size of the infarcts was ascertained after serial, transverse incisions across the ventricles were made. An infarct was found in every experiment in which the dog survived arterial ligation, and the infarcts were about the same in each group of experiments.

DISCUSSION OF RESULTS

In one series of sixteen experiments the sympathetic nervous system was removed, and, about seventeen days later, the descending ramus of the left coronary artery was ligated. In this series recovery took place in three instances, or about 20 per cent, and death occurred in thirteen, or 80 per cent. This mortality rate is about the same as that in the control group. If the cause of death could be attributed to pneumonia in Experiments 7 and 15, the mortality rate would be changed in no significant degree. These experiments indicate that sympathectomy does not reduce the mortality rate when the descending ramus of the left coronary artery is ligated, provided the interval between the two operations is about seventeen days.

In a series of eighteen experiments the sympathetic nervous system was removed, and, at the same operation, the descending ramus of the the left coronary artery was ligated. In this series recovery took place in six instances, or about 33 per cent, and death occurred in twelve, or

66 per cent. This mortality rate is somewhat less than that in the control group. The difference, however, may be of no significance. Pneumonia was found at autopsy in five dogs. It is probable that this complication was responsible for the death of one or more of these animals. If pneumonia, instead of arterial ligation, were the responsible factor in all of these experiments, the recovery rate would be increased to about 60 per cent. Ventricular fibrillation occurred in three of the eighteen experiments in the course of minutes after arterial ligation. This is about the same incidence as in the control group, namely, seven of thirty experiments.

CONCLUSIONS

1. Sympathectomy does not reduce the mortality of coronary arterial ligation, provided an interval of about seventeen days is allowed to elapse between the two operations.

2. Sympathectomy followed immediately by arterial ligation carries a slightly lower mortality than arterial ligation alone. This beneficial effect is transient. It is slight in degree, and, indeed, it may be questionable as to whether it exists. The heart is less irritable and the rate of contraction is slower after sympathectomy. In this respect the effect of sympathectomy resembles the effect of applying procaine to the surface of the heart.

3. The size of the infarcts caused by arterial ligation is not reduced by sympathectomy.

4. These studies indicate that sympathectomy cannot be considered an effective method of reducing mortality or size of infarcts resulting from acute coronary occlusion. It may have a slightly beneficial effect, but this effect, if present, is transient.

REFERENCES

1. Leriche, R., Herrmann, L., and Fontaine, R.: Ligature de la coronaire gauche et fonction cardiaque chez l'animal intact, *Compt. rend. Soc. de biol.* 107: 545, 1931.
2. Leriche, R., Herrmann, L., and Fontaine, R.: Ligature de la coronaire gauche et fonction du coeur après énérvation sympathique, *Compt. rend. Soc. de biol.* 107: 547, 1931.
3. Cox, W. V., and Robertson, H. F.: The Effect of Stellate Ganglionectomy on the Cardiac Function of Intact Dogs and Its Effect on Extent of Myocardial Infarction and on Cardiac Function Following Coronary Artery Occlusion, *AM. HEART J.* 12: 285, 1936.
4. Mendlowitz, M., Schauer, G., and Gross, L.: Hemodynamic Studies in Experimental Coronary Occlusion. III. Denervated Heart Experiments, *AM. HEART J.* 14: 21, 1937.
5. Schauer, G., Gross, L., and Blum, L.: Hemodynamic Studies in Experimental Coronary Occlusion. IV. Stellate Ganglionectomy Experiments, *AM. HEART J.* 14: 669, 1937.
6. Beck, C. S., and Mako, A. E.: Venous Stasis in the Coronary Circulation, *AM. HEART J.* 21: 767, 1941.

Special Article

NOMENCLATURE

DISEASES AND ABNORMALITIES OF THE BLOOD AND LYMPH VESSELS OF THE EXTREMITIES

DISEASES OF ARTERIES AND ARTERIOLES

I. Functional (vasomotor) conditions

A. Vasoconstrictor

1. Raynaud's syndrome (primary or idiopathic) (late stages secondary organic changes in arteries, skin, and subcutaneous tissues)
2. Raynaud's syndrome (secondary)
 - a. Traumatic vasospastic syndrome—pneumatic hammer disease, other types of repeated trauma.
 - b. Neurogenic—cervical rib, scalenus anticus syndrome, spondylitis, neuritis
 - c. Secondary to organic vascular disease—arteriosclerosis, thromboangiitis obliterans, syphilitic arteritis
 - d. Intoxications—nicotine, arsenic, ergot (early) lead?
 - e. Miscellaneous
3. Acrocyanosis
4. Cutis marmorata (early livedo reticularis)
5. Vasospasm secondary to
 - a. Lesions of peripheral nerve, brain, spinal cord
 - b. Thrombophlebitis
 - c. Acute arterial occlusion
 - d. Post-traumatic osteoporosis

B. Vasodilator

1. Erythromelalgia (erythermalgia)—primary
2. Erythromelalgia (erythermalgia)—secondary to
 - a. Polycythemia vera
 - b. Arteriosclerosis
 - c. Thromboangiitis obliterans
 - d. Trauma
 - e. Miscellaneous—secondary to fever, hyperthyroidism, alcoholism, neurocirculatory asthenia, menopause

II. Organic (structural) conditions

A. Occlusive (organic)

1. Generalized arteriosclerosis
 - a. Arteriosclerosis obliterans
 - b. Medial (Mönckeberg's) arteriosclerosis
 - c. Combined
2. Thromboangiitis obliterans
3. Periarteritis nodosa (essential periarteritis)
4. Temporal arteritis
5. Ergotism (early stages may be spastic)
6. Arteritis and arteriolitis secondary to
 - a. Infectious diseases
 - b. Local inflammatory processes
 - c. Hypertension
 - d. Lupus erythematosus disseminatus (including Libman-Sachs syndrome)
 - e. Idiopathic
7. Simple arterial thrombosis
 - a. Associated with infectious diseases
 - b. Associated with blood dyscrasias
 - c. Secondary to trauma or compression
 - d. Idiopathic
8. Abscess of the wall of artery (state organism)
9. Frost bite
10. Pernio
11. Livedo reticularis
12. Arterial embolism
 - a. Blood thrombus
 - b. Fat
 - c. Air
 - d. Bacterial
 - e. Neoplastic
 - f. Fungous
 - g. Inorganic substances

B. Nonocclusive

1. Aneurysm
 - a. Congenital
 - b. Syphilitic
 - c. Arteriosclerotic
 - d. Mycotic
 - e. Traumatic
 - f. Idiopathic
2. Arteriovenous fistula
 - a. Congenital
 - b. Traumatic

- c. Secondary to malignancy or other disease
- d. Mycotic
- 3. Congenital anomalies—other than fistula
- 4. Trauma and external compression (scalenus anticus syndrome)
- 5. Rupture
- 6. X-ray, radium, telangiectasia

NOTE. Ulceration or gangrene, when present, should be noted.

DISEASES OF VEINS

I. Vasomotor (functional)

Spasm

Following injury or disease of vein or accompanying artery or nerve

II. Organic (structural)

A. Obstructive

1. Thrombophlebitis and venous thrombosis (phlebothrombosis)
 - a. Primary
 1. Thromboangiitis obliterans
 2. Recurrent or migrating (without arterial lesions)
 3. Essential
 - b. Secondary to
 1. Mechanical injury (contusion, laceration, surgery)
 2. Muscular effort or strain
 3. Chemical injury (sclerosing agents, drugs, solutions for diagnosis)
 4. Inflammatory or suppurative lesions—Infectious diseases
 - a. Tuberculosis, syphilis, actinomycosis
 - b. Other bacteria (to be specified)
 5. Severe ischemia
 6. Chronic disease of vein wall (varices, phlebosclerosis) (Late complications—varicose or post-phlebitic ulcers)
 7. Blood dyscrasias (polycythemia vera, leucemia, pernicious anemia)
 8. Epidermophytosis (?)
2. Neoplastic invasion of vein
3. Venous compression, with or without thrombosis or thrombophlebitis, due to
 - a. Gravid uterus
 - b. Neoplasm
 - c. Aneurysm
 - d. Scar tissue
 - e. Scalenus syndrome
 - f. Fractures and dislocations
 - g. Increased intra-abdominal pressure (ascites, etc.)

B. Nonobstructive

1. Varicose veins (aneurysm)
 - a. Primary—congenitally incompetent valves
 - b. Secondary (to proximal obstructive lesions or pressure)
 - c. Secondary to phlebitic destruction of valves
 - d. Compensatory dilatation of collateral veins
2. Arteriovenous fistula
 - a. Congenital
 - b. Traumatic
 - c. Mycotic
 - d. Secondary to local disease
3. Aberrant position
4. Hypoplasia
5. Phlebectasia
6. Periphlebitis without thrombosis
7. Phlebosclerosis (not usually obstructive)
8. Rupture

TUMORS OF BLOOD VESSELS

A. Hemangioma

1. Simplex-telangiectasis
 - a. Nevus cinosus
 - b. Plexiform angioma
 - c. Hemangioma hypertrophicum
 1. Klippel-Trenaunay syndrome (hemangioma, varicose veins, osteohypertrophy)
2. Cavernosum
3. Racemosum (capillary)

B. Hypertrophic granulation tissue

C. Hemangio-endothelioma

D. Angiosarcoma

E. Glomus tumor

1. *Leiomyoma* of vessel wall

F. Endothelioma

G. Endothelial myeloma

H. Kaposi's disease

I. Sarcoma of blood vessel sheath

TUMORS OF LYMPH VESSELS AND LYMPH TISSUES

A. Lymphangioma

1. Simplex
2. Cavernosum
3. Cysticum (hygromas)
4. Secondary to incompetent valves

- B. Endothelioma
- C. Lymphoma (benign)
- D. Lymphocytoma
- E. Leucemia
- F. Lymphosarcoma
- G. Hodgkin's disease
- H. Reticulum cell sarcoma
- I. Sarcoma of sheath or capsule of lymph node

DISEASES OF PERIPHERAL LYMPH NODES AND LYMPH VESSELS

- I. Vasomotor (functional) ; none established
- II. Organic (structural)
 - A. Obstructive
 - a. Noninflammatory
 - 1. Primary lymphedema
 - a. Simple
 - b. Congenital
 - c. Hereditary (Milroy's disease)
 - d. Precox
 - 2. Secondary lymphedema due to
 - a. Surgical removal of lymph nodes
 - b. Neoplastic invasion of lymph nodes
 - c. X-ray treatment
 - b. Inflammatory
 - 1. Primary lymphangitis (cause unknown)
 - 2. Secondary lymphangitis due to
 - a. Filariasis
 - b. Trichophytosis
 - c. Local tissue injury or inflammation (lacerations, bites, burns, furuncles, other local infections, chemical, non-bacterial)
 - 3. Erysipelas
 - c. Calcification and fibrosis
 - d. Chylous ascites—secondary to obstruction of the thoracic duct (mention cause)
 - B. Nonobstructive
 - a. Lymphatic fistula
 - b. Unclassified

DISEASES OF MINUTE VESSELS

- A. Increased fragility
 - 1. Infectious purpura
 - a. Pneumonia
 - b. Septicemias, especially streptococcus

- c. Exanthemata
 - d. Other infectious diseases
 - 2. Toxic purpura
 - a. Arsenic
 - b. Phosphorus
 - c. Phenolphthalein
 - d. Numerous other drugs (individual susceptibilities)
 - e. Snake venom—insect venom
 - 3. Purpura due to avitaminosis C.K. (P.?)
 - 4. Hematogenic purpura
 - a. Thrombocytopenia
 - b. Leucemia
 - c. Aplastic anemia
 - 5. Purpura secondary to increased venous pressure
 - 6. Menstrual or menopausal purpura
 - 7. Senile purpura
 - 8. Idiopathic purpura
 - Henoch's purpura
 - Schoenlein's purpura
- B. Increased permeability
- 1. Angioneurotic edema
 - 2. Urticaria
 - 3. Sensitivity to physical agents
 - a. Mechanical irritation
 - b. Cold
 - c. Heat
 - 4. Local inflammation
 - 5. Vasomotor collapse
 - 6. Shocks
 - 7. Burns

CLASSES ACCORDING TO SEVERITY

- Class 1. Without symptoms
- 2. With symptoms—without organic changes
 - 3. With symptoms—with organic changes
 - 4. With loss of substance, trophic changes, gangrene, ulceration, etc.

The Nomenclature Committee of the Section for the Study of the Peripheral Circulation of the American Heart Association has prepared the first section of the Nomenclature of Diseases and Abnormalities of the Blood and Lymph Vessels. This section includes the blood and lymph vessels of the extremities only. The Committee has been aided by the advice and constructive criticism of all the Fellows of the Section and numerous other authorities in special divisions of the field.

Acknowledgment is especially due to the Executive Committee of the American Society for the Control of Cancer, which, under the Chairmanship of Dr. Frank Adair, compiled the subdivisions entitled "Tumors of the Blood Vessels" and "Tumors of the Lymph Vessels."

This Section is published at this time in order to provide a list of preferred and universal terms which may be used by authors, research workers, and all others interested in this field. It is recognized, however, that any nomenclature of this nature must be continuously regarded as in a fluid state, subject to frequent revision, and that this is not considered by the Committee to be a final listing.

The second section of this Nomenclature, including hypertension, nephritis, and associated diseases will continue in a state of preparation. The rapid changes taking place in the conceptions of the mechanisms involved in these diseases make it appear unwise to publish even a tentative nomenclature at this time. It is thought that several more years of study may well be needed for this problem, and, therefore, although the committee firmly believes that these two sections of the nomenclature should ultimately comprise a single integrated conception of diseases and abnormalities of the circulation, it will be helpful to present the section which has been most nearly completed at this time.

Nomenclature Committee of the Section for the
Study of the Peripheral Circulation of the
American Heart Association.

IRVING S. WRIGHT, M.D., Chairman
M. HERBERT BARKER, M.D.
NELSON W. BARKER, M.D.
NORMAN FREEMAN, M.D.
WILLIAM GOLDRING, M.D.
E. A. HINES, M.D.
IRVINE H. PAGE, M.D.
GERALD H. PRATT, M.D.
MILTON C. WINTERITZ, M.D.

Department of Clinical Reports

PRIMARY SARCOMA OF THE HEART

REPORT OF A CASE

DAVID R. WEIR, M.D., AND BENJAMIN C. JONES, JR., M.D.
CLEVELAND, OHIO

PRIMARY sarcoma of the heart occurs rarely enough to make the report of another case worth while. Diebold,¹ in 1930, and Yater,² in 1931, found forty-six cases in the literature. Twenty-nine additional cases were reported between 1930 and January, 1940, making a total of seventy-five cases. The diagnoses are given in Table I.

TABLE I

DIAGNOSIS	NO. OF CASES
Spindle cell sarcoma ²⁻⁴	17
Fibrosarcoma ^{2, 5-7, 27}	7
Leiomyoblastic sarcoma ⁸	1
Rhabdomyosarcoma (?) ⁹	1
Angiosarcoma ^{2, 10, 11}	5
Myxosarcoma ^{2, 12, 13}	6
Round cell sarcoma ^{2, 14-18}	19
Mixed cell sarcoma ^{2, 10}	5
Giant cell sarcoma ²	4
Lymphosarcoma ^{2, 20}	2
Unclassified sarcomas ^{2, 21-26}	8
Total	75

Under angiosarcoma are included the two cases of Choisser and Ramsey¹¹ which they regard as instances of typical Kaposi tumors and have called angioreticuloendotheliomas. They believe that careful review of the microscopic sections in all reported cases would disclose other tumors that could be put into the same classification.

Larson and Sheppard's⁹ case of rhabdomyosarcoma in a 37-year-old woman is the only one of several which have been reported in which reasonably good photomicrographic evidence is presented to confirm that diagnosis. However, even in their case the evidence is not unequivocal.

In the twenty-eight cases which have been reported since 1930, the site of origin was mentioned in twenty-four. In twelve of these the tumor arose from the right auricle. This corroborates Yater's² statement that the right auricle is by far the most common site of origin. The presence or absence of metastases was noted in twenty-one of the

From the Department of Medicine and the Institute of Pathology, University Hospitals, and Western Reserve University.

Received for publication June 17, 1940.

twenty-eight cases, and thirteen of these twenty-one showed definite metastases. Diebold and Yater found that metastases were noted in only fifteen of their forty-six cases.

CASE REPORT

A 60-year-old white man entered the Lakeside Hospital complaining of dyspnea of eight weeks' duration. For nine years before entry he had come on numerous occasions to the Outpatient Department complaining of a variety of seemingly neurotic symptoms. Except for slight hypertension (168/98), which was discovered eight years before admission, there had been no abnormal physical signs. About eight weeks before admission he began to have definite shortness of breath on exertion, without orthopnea or paroxysmal nocturnal dyspnea. This was associated with slight precordial pain. Two electrocardiograms which were taken at that time showed left axis deviation, but no evidence of myocardial infarction. The dyspnea continued, and he gradually developed cough and loss of appetite. Four weeks before entry the cough became productive of bloody sputum, and râles were heard at the bases of the lungs. A roentgenologic examination five days before admission showed small areas, measuring up to 2 cm. in diameter, of increased density scattered throughout both lungs.

At the time of admission to the hospital, physical examination revealed a well-developed, well-nourished white man who was having moderate respiratory distress. There was slight cyanosis of the lips and finger tips. The heart was somewhat enlarged to the left, and the aortic second sound was accentuated. No significant murmurs were heard. Scattered patches of râles were heard throughout both lungs. The breath sounds were diminished over the left apex posteriorly, but there was no evidence of consolidation of the lungs. The edge of the liver was slightly tender and was palpable 2 cm. below the costal margin. The abdomen was otherwise normal. The prostate was moderately enlarged, symmetrical, and without nodules. There was no fluid in any of the body cavities, and no peripheral edema was present.

The temperature was 37.7° C.; the pulse rate, 100; the respiratory rate, 23; and the blood pressure, 134/70.

The urine was normal. The erythrocyte count was 3,330,000; the hemoglobin was 66 per cent, and the leucocyte count was 12,250, with 77 per cent polymorphonuclear leucocytes. The Kline exclusion test was negative. The blood urea nitrogen was 21 mg. per 100 c.c. Smears of the sputum showed a variety of cocci and many budding, yeastlike organisms. The sputum cultures yielded yeasts, *Streptococcus hemolyticus*, *Streptococcus viridans*, and *Staphylococcus albus*.

A roentgenologic examination of the chest on the first hospital day showed a questionable increase in the size of the lesions in the lungs, and it was thought that many of the lesions had a distinctly nodular appearance.

On the day after admission, auricular fibrillation set in, with a ventricular rate of 104 and a radial pulse rate of 80. The diagnosis was confirmed by an electrocardiogram. The following morning at 9 o'clock, the auricular fibrillation was still present. At about 11 A.M. the patient suddenly became extremely dyspneic. The pulse rate was found to be 180 and the pulse was regular. An electrocardiogram showed auricular flutter. In spite of emergency measures he died about twenty minutes after the onset of the flutter.

POST-MORTEM EXAMINATION

The essential autopsy observations were limited to the heart, lungs, and adrenals.

The heart was firmly adherent to the pericardium; together, they weighed 970 Gm. From the medial and anterior aspects of the wall of the interior of the right

atrium there arose a large, firm, yellowish-brown papillary tumor which completely filled the right auricular appendage, extended over the anterior leaflet of the tricuspid valve, and up the superior vena cava as far as the ostium of the left subclavian vein. The main tumor measured $10 \times 3 \times 2.5$ cm. and had invaded the myocardium of the auricles and right ventricle. There was no endocarditis or valvulitis.

The parenchyma of both lungs was studded with innumerable discrete and confluent grayish-purple nodules of tumor tissue, measuring up to 2 cm. in diameter. No single, large, tumor mass was found in either lung, and no nodules were seen arising from the larynx, trachea, or bronchi.

The medulla of each adrenal was infiltrated by tumor tissue, which, in one, measured 2 cm., and, in the other, 1.5 cm. in diameter.

Microscopic Examination.—Sections through various portions of the tumor, stained with hematoxylin and eosin, showed small groups, slightly whorled and interlacing cords, and solid sheets of cells. The cells were supported by a moderate amount of stroma. There were extensive invasion and destruction of the myocardium and epicardium. Many small and large areas of necrosis and hemorrhage were present. From place to place throughout the tumor there was striking pleomorphism. However, the predominating type of cell was of moderate size, elongated, with homogeneous acidophilic cytoplasm. The nuclei were round or oval and occupied from one-third to one-half of the cell volume. They were vesicular and contained a fine network of chromatin and one or two indistinct nucleoli. Numerous normal mitotic figures were present, but there were no multinucleated cells. In some areas the cells were completely undifferentiated and resembled both epithelium and reticulum cells. In other areas they were predominantly spindle-shaped, with sausage-shaped nuclei, long, tapering, cytoplasmic processes, and parallel bundles of extracellular fibrils. Scattered throughout the tumor were a few large cells with vesicular, hypochromatic nuclei. These contained intracellular fibrils, as shown by the phosphotungstic acid-hematoxylin stain, and resembled myoblasts.

Sections stained by the van Gieson and azocarmine methods showed that the supporting stroma of the tumor contained only a small amount of collagen. Sections of the tumor stained by the phosphotungstic acid-hematoxylin method failed to reveal cross striations in any of the tumor cells.

Microscopic examination of the tumor nodules which were found in the lungs and adrenals showed that they were histologically identical with those in the heart. Throughout the lungs, tumor was found in the peribronchial tissues and, in several sections, was found to have grown through the bronchial wall into the lumen. In these areas there was slight hemorrhage into the bronchi.

A clinical diagnosis of carcinoma metastatic to the heart and lungs, primary source undetermined, was made. The tumor was thought to involve the heart because of the unexplained cardiac failure and the appearance of auricular fibrillation and auricular flutter for no apparent reason. Except for mild hypertension, no clinical evidence of the common forms of heart disease could be found.

The largest tumor was in the right atrium. The direct and irregular invasion of neighboring structures was more like the growth of a primary than a secondary tumor of this region. The focalized, nodular character of the tumors in the lungs and adrenals was what would be expected of metastatic lesions. The tumor was histologically the same everywhere. The gross and microscopic character of the various lesions indicated that the tumor was primary in the heart. The involvement of the lungs and of the two adrenals was caused by blood vascular dissemination.

The sarcomatous nature of the neoplasm was evident. The absence of cross striations and the fact that no rods were found in the large, spherical cells excluded

rhabdomyomatous tumor. Because of the presence of fibrils, which were like myofibrils, because of the fibrillar content of the cytoplasm of the large, spherical cells, and because of the nuclear forms in the elongated cells, Dr. Howard T. Karsner classified this sarcoma as a leiomyosarcoma. This view was shared by several other experienced pathologists who saw the material, but not by one pathologist, who believed that it was a mesothelioma. Although it undoubtedly originated in the right atrium, the exact point of origin could not be ascertained.

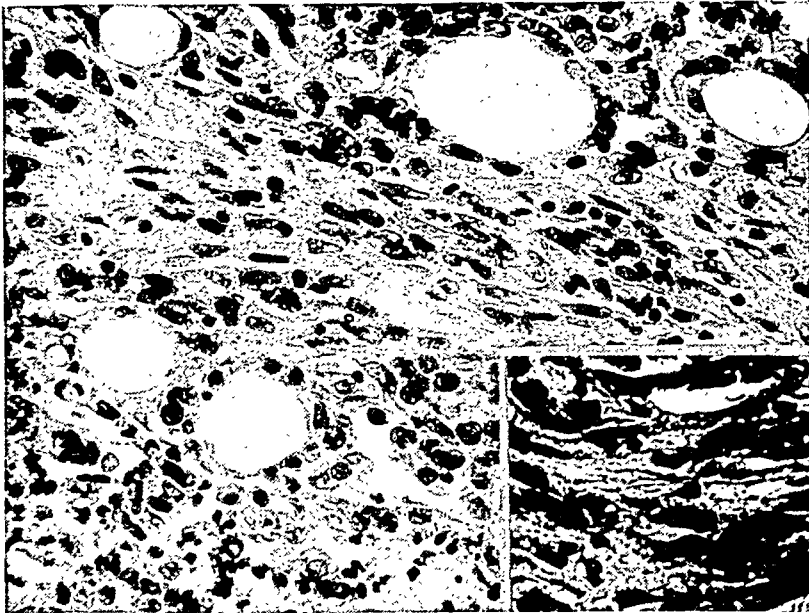


Fig. 1.—Larger field shows invasion of epicardial fat by tumor made up of elongated cells with "sausage-shaped" nuclei. Cytoplasm shows barely visible longitudinal fibrils. Hematoxylin and eosin ($\times 450$). Smaller field shows, in the middle, definite longitudinal fibrils. Phosphotungstic acid hematoxylin ($\times 540$).

COMMENT

The clinical diagnosis of primary or secondary tumor of the heart has been made fairly frequently in recent years. The majority of these diagnoses were made by means of the following criteria, as summarized by Yater and others: unexplained congestive heart failure, unexplained electrocardiographic changes, such as heart block and nodal rhythm, unexplained auricular fibrillation and auricular flutter, signs of acquired pulmonic stenosis, other signs of obstruction of blood flow through the heart without obvious cause, failure to respond to digitalis, bloody pericardial effusion, and roentgenologic evidence of irregularities of the cardiac shadow. When a primary malignant tumor is known to exist elsewhere in the body, metastatic involvement of the heart may be more readily suspected when some of the above manifestations are present.

SUMMARY

This case of primary sarcoma of the heart brings to seventy-six the total number of cases of this disease now on record. This includes

two cases in which the tumor was regarded as an angioreticoendothelioma. Various signs and symptoms led to a correct clinical diagnosis of cardiac neoplasm.

REFERENCES

1. Diebold, O.: Über das primäre Herzsarkom, *Ztschr. f. Kreislaufforsch.* 22: 785, 1930.
2. Yater, W. M.: Tumors of the Heart and Pericardium, *Arch. Int. Med.* 48: 627, 1931.
3. Holer, F.: Primäres metastasierendes Spindelzellensarkom des rechten Herzvorhofs, Frankfurt. *Ztschr. f. Path.* 51: 242, 1937.
4. Denecke, K.: Ein primäres Herzsarkom und seine klinischen Erscheinungen, *Med. Klin.* 26: 1820, 1930.
5. Popp, L.: Über die Herzgeschwülste in Verbindung mit einem Falle von Sarkom des rechten Vorhofohres, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 46: 23, 1932.
6. Willius, F. A.: Primary Fibrosarcoma of the Right Auricle, *Proc. Staff Meet., Mayo Clin.* 13: 331, 1938.
7. Fiddler, R. S., Kissane, R. W., and Koons, R. A.: Primary Fibrosarcoma of the Heart, *AM. HEART J.* 13: 736, 1937.
8. Weese, K.: Cited from Rindt and Schwartz.¹⁴
9. Larson, C. P., and Sheppard, J. A.: Primary Rhabdomyoma of the Heart With Sarcomatous Extensions, *Arch. Path.* 26: 717, 1938.
10. Hoyer, T. F., and Kemp, R. P.: Malignant Hemangio-Endothelioma of the Heart, *J. Path. & Bact.* 43: 511, 1936.
11. Choisser, R. M., and Ramsey, E. M.: Angioreticoendothelioma (Kaposi's Disease) of the Heart, *Am. J. Path.* 15: 155, 1939.
12. Fenster, E.: Primäres malignes Myxom des Herzens mit Metastasen, Frankfurt. *Ztschr. f. Path.* 45: 565, 1933.
13. Müller, W.: Über polypöse, bösartige, metastasierende Endokardgewächse und gewächsartige Thromben des linken Herzvorhofs, *Virchows Arch. f. path. Anat.* 284: 105, 1932.
14. Rindt, H., and Schwarz, H.: Über Herzsarkom, *Ztschr. f. Krebsforsch.* 44: 66, 1936.
15. Poujol, G., and Barone, R.: Un cas de Sarcome Primitif du Coeur a forme infiltrante. *Bull. Assoc. franç. p. l'étude du cancer* 26: 64, 1937.
16. Nath, V.: A Case of Primary Sarcoma of the Heart, *Indian M. Gaz.* 66: 673, 1931.
17. Morris, J. J.: Primary Sarcoma of the Heart, *J. Lab. & Clin. Med.* 18: 935, 1933.
18. Cossio, P., and Berconsky, I.: Sarcoma primitivo pericardiomicrocardico, *Rev. argent. de cardiol.* 5: 172, 1938.
19. Martin, W. C., Tuohy, E. L., and Will, C.: Primary Tumor of the Heart (Entrance of the Pulmonary Artery), *AM. HEART J.* 17: 728, 1939.
20. Cracium: Cited from Rindt and Schwartz.¹⁴
21. Leriche and Bauer: Cited from Rindt and Schwartz.¹⁴
22. Haban, G.: Cited from Rindt and Schwartz.¹⁴
23. Shelburne, S. A.: The Diagnosis of Tumors of the Heart and Pericardium, *Texas State J. Med.* 31: 433, 1935. Primary Tumors of the Heart, *Ann. Int. Med.* 9: 340, 1935.
24. Reeves, J. M., and Michael, P.: Primary Tumor of the Heart, *AM. HEART J.* 11: 233, 1936.
25. Barnes, A. R., Beaver, D. C., and Snell, A. M.: Primary Sarcoma of the Heart, *AM. HEART J.* 9: 480, 1934.
26. Cabot Case: Primary Sarcoma of the Right Auricle, *New England J. Med.* 215: 1082, 1936.
27. Jackson, M. N., and Jacobson, J. N.: Primary Fibrosarcoma of the Heart, *Lancet* 2: 740, 1939.

Department of Reviews and Abstracts

Selected Abstracts

Graybiel, A., and White, P. D.: Diseases of the Heart. A Review of Significant Contributions Made During 1940. Arch. Int. Med. 67: 1061, 1941.

This is the annual review of diseases of the heart in this journal. Particular emphasis is given to the medical problems associated with the World War, especially the examination of the heart in the selection of military personnel. Attention is directed also to neurocirculatory asthenia.

McCULLOCH.

Boyd, T. E., and Patras, Mary C.: Variations in Filling and Output of the Ventricles With the Phases of Respiration. Am. J. Physiol. 134: 74, 1941.

A method of cardiometric recording, designed for use with the chest closed, is described. It maintains on the ventricles an external pressure which is always approximately equal to intrathoracic pressure, varying in the normal manner with the phases of respiration. It can be alternatively used in such a way that the ventricles are left under constant atmospheric pressure.

With the ventricles under atmospheric pressure, diastolic volume and stroke output diminish markedly with inspiration (confirming the findings of earlier investigators). These are abnormal effects, due to the artificially high resistance against which the ventricles are filled.

With the ventricles under intrathoracic pressure, combined diastolic volume and stroke output of the two ventricles are augmented with inspiration. These effects are most pronounced when inspiration is deep and prolonged. They are relatively small in quiet eupneic breathing and are minimal when breathing is rapid and shallow.

AUTHORS.

Keys, A.: Estimation by the Foreign-Gas Method of the Net (Systemic) Cardiac Output in Conditions Where There Is Re-Circulation Through the Lungs. Am. J. Physiol. 134: 268, 1941.

Some fundamental kinetics have been analyzed for the gas absorption by the blood in the foreign-gas methods for estimation of the cardiac output in man. The discussion applies specifically to the acetylene method but the conclusions apply to the other foreign gases.

It is shown that the absorption proceeds according to an equation of the first order, and the mathematical analysis is developed accordingly.

The condition where recirculation occurs in the lungs is analyzed in detail, and equations are derived for the proper computation of the true systemic circulation in such cases. The variables involved are the concentrations of the foreign gas in the gas samples from the lung-bag system, the fraction of blood recirculated, the short-circuit time, and the total time between samples. Graphs for computations with these variables are presented.

It is shown that recirculation through the lungs in the presence of patent ductus arteriosus or interventricular septal defects does not necessarily introduce a serious error and that this error may be estimated.

It is shown that recirculation of blood from the coronary system cannot introduce an appreciable error.

The error resulting from the common assumption that the absorption of the foreign gas is linear with time is discussed and shown to be ordinarily small. Means are provided to estimate this error by equations and a graph.

Timing of the gas sampling is discussed. It is shown that the second sample may be taken later than is frequently believed possible. When there is recirculation, the first sample should be delayed four to five seconds, but it is shown that two to three seconds are not critical.

Results of forty-one studies on twenty-two patients with patent ductus arteriosus are presented in summary form. The average cardiac index is normal or close to it in this group.

It is indicated that many criticisms of the foreign-gas methods are invalid because they are based on quantitative misconceptions. On the other hand the importance and difficulty of physiologic standardization in cardiac output measurements are frequently underestimated.

AUTHOR.

Holt, J. P.: The Collapse Factor in the Measurement of Venous Pressure. The Flow of Fluid Through Collapsible Tubes. *Am. J. Physiol.* 134: 292, 1941.

Right auricular and peripheral venous pressures were measured in dogs breathing from a chamber in which the pressure varied between 20 cm. of water above atmospheric and 20 cm. below. It was shown that, when auricular pressure was decreased greatly, and in some cases when auricular pressure was increased slightly, the peripheral venous pressure remained constant. In most cases when auricular pressure increased, the peripheral venous pressure was increased.

The flow of water through collapsible tubes such as the jugular vein of the dog was studied in a model. When fluid is flowing through a partially collapsed tube, increasing the pressure on the upstream side of the partially collapsed segment decreases the resistance to flow through the collapsible segment and increases the rate of flow, whereas lowering the pressure on the downstream side of the collapsible segment increases the resistance to flow through the collapsible segment and either does not change the rate of flow or decreases it slightly. An increase in the jacket pressure around the collapsible tube increases the resistance to flow through the collapsible segment and decreases the rate of flow.

As a collapsible tube, having fluid flowing through it, starts to collapse, it pulsates; as it becomes more collapsed, the pulsation increases in rate; and on further collapse the pulsation apparently disappears.

The length of the collapsible tube is not important in controlling the length of the partially collapsed segment. It appears to be necessary only that the tube be long enough and relaxed enough to collapse in order to give the results described, and any length of collapsible tube greater than this length acts merely as a dilated or rigid tube.

AUTHOR.

Pitts, R. F., Larrabee, M. G., and Bronk, D. W.: An Analysis of Hypothalamic Cardiovascular Control. *Am. J. Physiol.* 134: 359, 1941.

Stimulation of the hypothalamus of the anesthetized cat with brief repetitive condenser shocks of moderate intensity leads, after a latency of less than 0.1 second, to an abrupt increase in activity of sympathetic nerves to the heart and blood ves-

sels. This activity ceases equally abruptly when stimulation is stopped, and for a variable period thereafter all spontaneous activity in these nerves is inhibited. There is no evidence under the conditions of our experiments that any sympathetic after discharge results from hypothalamic stimulation. Blood pressure begins to rise one to two seconds after the start of hypothalamic stimulation and may continue to rise and remain elevated several seconds after stimulation is stopped. The delay in the rise of blood pressure and the prolongation of the rise result from latency and inertia of the sympathetic effector, not from any corresponding delay or persistence of neural activity.

An increase in intensity or frequency of hypothalamic stimulation increases the magnitude and duration of the rise in blood pressure. This increased effector response is brought about by an increase in the number of sympathetic motor neurones set into activity and by an increase in the frequency of response of each neurone.

Multiple pathways descend from both sides of the hypothalamus to make connection with each sympathetic motor neurone. The frequency of response of the neurone is a function of the number of these pathways excited and of the frequency at which they are excited.

While stimulation of the lateral and posterior portions of the hypothalamus yields responses of greater magnitude, no qualitative differences have been noted on stimulation of the preoptic, tuberal, or mammillary divisions.

The buffer reflexes which control the spontaneous sympathetic outflow from the medullary centers also moderate the outflow induced by hypothalamic stimulation. Activation of the buffer afferents may inhibit all response of sympathetic motor neurones to hypothalamic stimulation or reduce the number of these neurones responding. Similarly the frequency of response of any single neurone may be reduced or the response entirely abolished by activation of the buffer afferents. The buffer afferents impress a pulse modulation upon mild increases of sympathetic activity which result from hypothalamic stimulation in exactly the same way that they modulate spontaneous sympathetic outflow. These facts are interpreted as indicating that sympathetic responses from hypothalamic stimulation are mediated through medullary sympathetic centers, not by direct connection of descending hypothalamic pathways with sympathetic motor neurones.

The frequency of firing of a sympathetic motor neurone in response to hypothalamic stimulation is determined by the level of excitation maintained by the hypothalamic volleys, the time course of the recovery cycle, and the degree of activity of inhibitory afferents at some critical point between hypothalamus and motor neurone.

AUTHORS.

Brace, D. E., Scherf, D., and Spire, L. J.: The Effect of Cyclopropane on the Blood Pressure, Stroke-Volume, and Heart Size of the Dog. *Anesthesiology* 2: 261, 1941.

The blood pressure and cardiac plethysmograms were registered in dogs during and immediately after the administration of cyclopropane for 4.5 to five minutes.

The blood pressure showed a very slight initial rise and then a slow fall lasting about two minutes. During the third and fourth minutes the blood pressure began to rise, and it continued to rise for a few minutes after the anesthesia was stopped. Then it fell gradually to its original level. After the anesthesia was discontinued for twenty seconds, a steep rise in the pressure was followed by a fall of ten seconds' duration in 50 per cent of the experiments.

The amplitude of the pulse waves in the blood pressure tracings diminished during the administration of cyclopropane and rose soon after it had been stopped.

During the administration of the drug, the plethysmogram showed that a marked dilation of the heart occurred in diastole and a less marked dilation in systole. Although the output increased, slight stasis occurred in the heart. About twenty seconds after the administration of cyclopropane was stopped, systole became more forcible and the cardiac volume smaller in systole and diastole. The changes during the systolic phase were more rapid. The stroke volume increased markedly.

Arrhythmias were never observed. Cardiac alternans appeared frequently.

AUTHORS.

Wearn, Joseph T.: Observations on the Morphology and Functions of Some of the Components of the Coronary Circuit. William Sidney Thayer and Susan Read Thayer Lectures. Bull. Johns Hopkins Hosp. 68: 353, 1941.

Factors influencing the volume and distribution of coronary blood flow are as yet imperfectly understood. Krogh has demonstrated the intermittence of blood flow in the smaller vessels in skeletal muscle. Richards and Schmidt observed an intermittence of flow in the frog's glomeruli, and Bordley, Grow, and Sherman have observed an intermittent flow in the capillaries of the skin. Pulmonary vessels behave similarly. In our laboratory during the past ten years numerous attempts have been made to get evidence of intermittent flow in the heart. To date, however, the evidence from injection experiments in living hearts indicates that the heart utilizes all of its capillaries at all times. The slowly beating heart and the rapidly driven heart under increased load, when injected with a dye, usually show a complete injection of all available capillaries. These experiments, which are still in progress, are by no means final, but the results so far suggest that intermittence of flow does not occur in the coronary circuit.

AUTHOR.

Wearn, Joseph T.: Alterations in the Heart Accompanying Growth and Hypertrophy. William Sidney Thayer and Susan Read Thayer Lectures. Bull. Johns Hopkins Hosp. 68: 363, 1941.

The changes occurring in hypertrophy increase the distance over which oxygen and metabolites must travel, and in the absence of any obvious compensatory mechanism, such as an increase in the myoglobin content, or an increase in the percentage saturation of oxygen in the coronary venous blood, one might raise the question as to whether hypertrophy is an actual hindrance to the efficiency of the heart. Whether a compensatory increase in the volume of blood flow in the coronary circuit occurs with hypertrophy is unknown.

AUTHOR.

Dally, J. F. Halls: Life and Times of Jean Nicholas Corvisart. Proc. Roy. Soc. Med. 34: 239, 1941.

This historic biographic sketch of Corvisart in medieval medicine describes his contributions to the development of the modern study of cardiology.

McCULLOCH.

Schecter, A. E., Wiesel, B. H., and Cohn, C.: Peripheral Circulatory Failure in Diabetic Acidosis and Its Relation to Treatment. Am. J. M. Sc. 202: 364, 1941.

Eight patients with diabetic acidosis were studied. Initially elevated hemoglobin, hematocrit and serum protein with a decrease following administration of fluids showed the presence of dehydration and hemoconcentration. Peripheral blood flow

in the hand, as measured by the plethysmograph, was reduced. Venous oxygen saturation was high in the presence of marked reductions in peripheral blood flow. Physiologic evidence presented supports the clinical impression of the existence of peripheral circulatory failure in diabetic acidosis. The existence of an unusually high venous oxygen saturation in the presence of a reduced peripheral blood flow suggests a failure of oxygen utilization by the tissues. Possible causes suggested for the failure of oxygen utilization are (1) inability to utilize carbohydrate; (2) ketosis, or (3) acidosis. These findings point out the existence of a histotoxic as well as a stagnant anoxia in the peripheral circulatory failure of diabetic acidosis.

The importance of the prompt restoration of blood volume and the maintenance of adequate circulation in the treatment of diabetic acidosis is stressed.

AUTHORS.

Cos, A. J., Jr., and Dock, W.: The Capacity of the Renal Vascular Bed in Hypertension. J. Exper. Med. 74: 167, 1941.

By using kerosene and avoiding post-mortem rigor, one can obtain perfusion rates in kidneys nearly five times faster than those reported by observers who perfused kidneys immediately post mortem with saline solution, only half as viscous as kerosene.

The results obtained by kerosene perfusion indicate possible renal blood flow 50 to 100 per cent greater than that measured by Smith and his co-workers in living men by diodrast clearance under normal conditions, and about as high as those observed in febrile subjects. Like the diodrast method, kerosene perfusion shows a striking decrease in renal vascular bed between early maturity (age 18 to 35) and senescence (45 to 60). This decrease is about 25 per cent.

Most kidneys from patients with hypertension without uremia have vascular beds in the normal range, but a few show great decreases in capacity for blood flow. This evidence is interpreted as another indication that renal arteriosclerosis is often a result, rarely a cause of hypertension. Significant occlusion of large renal arteries is rare.

Uremia due to amyloid may occur with no significant decrease in renal vascular bed, but the uremia of renal sclerosis, glomerulo- or pyelonephritis is associated with reduction of vascular bed to very low levels.

AUTHORS.

Dock, W.: The Capacity of the Coronary Bed in Cardiac Hypertrophy. J. Exper. Med. 74: 177, 1941.

After the elimination of vascular rigor, perfusing human hearts with kerosene under pressure post mortem gives values for coronary flow which seem to be an index of the maximum possible flow during life. This is 3.1 c.c. per gram per minute at 100 mm. Hg in normal men under 40. It is 35 per cent lower in the hearts of those 60 to 80 years old and also falls in hypertrophied hearts. In old people it is 30 per cent lower in hearts over 600 Gm. than in those under 350; in patients 40 to 60 years old it is 37 per cent less in hearts over 600 as compared with those under 350 Gm.

In discussion it is brought out that, while the decrease in coronary capacity associated with age or hypertrophy may play a part in predisposing some hearts to congestive failure, there is no evidence that the hypertrophied heart has an inadequate oxygen supply or that its fibers are too thick for adequate oxygen diffusion. Congestive failure cannot be ascribed to anoxia except in the presence of severe anemia, coronary occlusion, or tachycardia with low blood pressure. Decrease in

perfusibility with age and growth may be a perfectly normal adaptation to the needs of the tissue; the perfusibility of the heart of the young adult is about half that of an infant of 2 years.

AUTHOR.

Wolf, S., and Hardy, J. D.: Studies on Pain. Observations on Pain Due to Local Cooling and on Factors Involved in the "Cold Pressor" Effect. J. Clin. Investigation 20: 521, 1941.

Pain due to local cooling is altogether separate from the sensation of cold itself. It is apparently mediated through small, nonmyelinated fibers of class C. Its intensity, however, depends directly upon the degree of cooling. The stimulus required for the production of "cold pain" may be found in the thermal gradient in the tissues of the immersed hand. It is possible that this stimulus brings about a painful vasospasm in the part. Relaxation of this local vasospasm may occur as the thermal gradient is decreased, thus accounting for "adaptation." It appears that the "cold pressor" effect is a measure of reaction to pain.

AUTHORS.

Abramson, D. I., and Fierst, S. M.: The Peripheral Vascular Response to Exercise in the Hyperthyroid State. J. Clin. Investigation 20: 517, 1941.

The post-exercise blood flow repayment was generally found to be much greater in the hyperthyroid state than in the period following subtotal thyroidectomy.

A correlation was apparent between the level of oxygen consumption and the magnitude of the excess blood flow elicited by the exercise.

Exercise places a much greater load upon the circulation in hyperthyroidism than in the normal state.

AUTHORS.

Dressler, M., and Moskowitz, S. N.: Fetal Electrocardiography and Stethography. Am. J. Obst. & Gynec. 41: 775, 1941.

Forty gravidas were studied routinely in the last two months of pregnancy to determine the diagnostic significance of the fetal electrocardiogram and the fetal stethogram, separately and simultaneously, in evaluating the presence of a viable fetus. The individual value of each method was enhanced by the combined study.

The fetal stethogram was positive in 100 per cent of the cases, the fetal electrocardiogram in 80 per cent.

The stethogram is helpful in studying the rate, rhythm, and regularity of fetal heart sounds, the systolic and diastolic phases, murmurs, the uterine souffle, and fetal movements. The intensity of fetal heart sounds depends upon the site at which the microphone is applied, and upon maternal and fetal conditions. In most cases the second sound is louder than the first. As a rule, diastole is longer than systole, but in the presence of fetal tachycardia they may become equal.

The electrocardiogram is valuable in the presence of positive tracings. The absolute diagnosis of fetal presentation is made by the fetal electrocardiogram. If the waves are negative, a vertex presentation is present; if positive, a breech presentation is present. In the presence of an equal systolic and diastolic phase, the first sound is recognized by its relationship to the R wave of the fetal electrocardiogram.

The factors involved in negative electrocardiograms are a nervous mother, a small fetus, maternal tachycardia, and possibly fetal sinus arrhythmia.

The combined tracings give permanent records of documental value. The maternal electrocardiogram is also recorded.

The use of fetal electrocardiography and fetal stethography for routine and consultation purposes is recommended because of the simple procedure involved and the ease with which tracings can be interpreted.

A case of breech presentation with positive tracing in Lead I, and variations in maternal and fetal rate is discussed.

AUTHORS.

Hoff, H. E., Nahum, L. H., and Kaufman, W.: The Nature of Leads I and III of the Electrocardiogram. *Am. J. Physiol.* 134: 390, 1941.

Lead I records the algebraic summation of the anterior levocardiogram and the posterior dextrocardiogram.

Lead III records the algebraic summation of the anterior dextrocardiogram and the posterior levocardiogram.

AUTHORS.

Nahum, L. H., Hoff, H. E., and Kaufman, W.: Formation of the R Complex of the Electrocardiogram. *Am. J. Physiol.* 134: 384, 1941.

The R complex of the electrocardiogram results from the algebraic summation of the initial portions of the dextro- and levocardiograms.

When the R complex is upright, its initial deflection is the upstroke of the dextrocardiogram, while the downstroke is produced by the onset and development of the levocardiogram.

When the R complex is directed downward, the downstroke is the initial portion of the levocardiogram, while the upstroke is produced by the onset and development of the dextrocardiogram.

The amplitude of the R complex varies with the interval separating onset of the dextro- and levocardiograms. The maximum amplitude is limited by the amplitude of the component dextro- or levocardiograms.

AUTHORS.

Taquini, Alberto C.: The Electrocardiogram in Experimental Chagas Disease. *Rev. argent. de cardiol.* 8: 115, 1941.

Inoculation of puppies with *Tripanozoma Cruzii* is followed by marked electrocardiographic alterations—arrhythmias and changes in auricular and ventricular complexes, evidence of myocardial damage.

AUTHOR.

Steele, J.: Evidence for General Distribution of Peripheral Resistance in Coarctation of the Aorta: Report of Three Cases. *J. Clin. Investigation* 20: 473, 1941.

Review of the knowledge of levels of arterial pressure in 217 cases of coarctation of the aorta makes untenable the assumption that increase in peripheral resistance is situated in the upper half of the body only.

In two of three cases of coarctation of the aorta, diastolic pressure has been shown by intra-arterial measurement to be elevated above 100 mm. Hg in the femoral as well as in the radial arteries. This is interpreted as evidence of general increase in arteriolar tone throughout the body.

In so far as the distribution of peripheral arteriolar resistance is concerned, arterial hypertension in coarctation of the aorta does not differ from the common forms of arterial hypertension.

AUTHOR.

Liebow, A. A., and McFarland, W.: "Corrected Transposition," and Persistent Rudimentary "Right Aorta" as Evidence in Support of Spitzer's Theory. *Arch. Path.* 32: 356, 1941.

In this study Spitzer's theory has received confirmation (1) in the analysis of a very complex anomaly, bulboventricular inversion with transposition of the great vessels, and (2) in suggestive direct evidence of the existence of a homologue of the reptilian right aorta, which is recorded for the first time as observed in an anomalous human heart.

AUTHORS.

Hahn, P.: Reflections on the Mechanism of Spontaneous Rupture of the Heart. *Cardiologia* 5: 33, 1941.

In a case of mitral disease, which developed over several years and ended with massive pulmonary embolism, a rupture of the endo- and myocardium in the vicinity of the right auricle was found. Blood had infiltrated into the subepicardial tissue.

The histologic examination of the site of the rupture revealed no prior lesion that could have explained the tear: the in toto definitely hypertrophic wall of the ventricle showed decreased thickness of the myocardium between the trabecles; the fibers of the myocardium were, however, unchanged. Microscopic examination of other parts of the heart revealed no damage.

Apart from mitral stenosis (without fresh inflammatory changes) and hypertrophy, the heart was in good condition. This permits the assumption that the overpressure in the ventricle caused by the pulmonary embolism was responsible for the rupture.

After consideration of the physical and hemodynamic appearances, an attempt was made to account for the potentials concerned in the genesis of the rupture.

This consideration showed the complexity of these laws and the experimental difficulties to be overcome in order to clear up the problem. With regard to the right of the heart the data so far at our disposal are very incomplete; all former experiments had reference to large circulation, which is more amenable to research.

AUTHOR.

Blumgart, H. L., Schlesinger, M. J., and Zoll, P. M.: Multiple Fresh Coronary Occlusions in Patients With Antecedent Shock. *Arch. Int. Med.* 68: 181, 1941.

In a series of 350 cases, eleven were found in which the heart showed multiple fresh coronary arterial occlusions, all occurring in the presence of shock. Of these, eight were instances of multiple thrombosis and three were instances of multiple fresh nonthrombotic occlusions. The shock was due to conditions other than myocardial infarction in eight of these eleven cases. In all, the patients were elderly and gave marked clinical and pathologic evidence of coronary disease. In addition, a single fresh coronary occlusion was found in thirty-eight cases, in twenty-two of which it was due to a thrombotic and in sixteen to a nonthrombotic mechanism. Shock due to noncardiac causes or congestive failure was present in approximately half of these cases.

Shock, no matter how produced, may lead in elderly patients, particularly in those showing evidence of coronary arteriosclerosis, to the development not only of single, but often of multiple, fresh coronary arterial occlusions. To avert such disastrous complications, the manifestations of shock, such as lowering of blood pressure, tachycardia, and dehydration, must be combated with particular vigor in these patients.

AUTHOR.

Simburg, E. J.: Spontaneous Cardiac Rupture. *Canad. M. A. J.* 45: 112, 1941.

Two cases of spontaneous cardiac rupture are reported from our own service. The clinical and pathologic findings agree essentially with those of several larger investigations. The latter are discussed in some detail.

AUTHOR.

Jason, R. S.: Insufficiency of the Aortic Valve Due to Syphilis: A Study of Its Genesis. *Arch. Path.* 32: 409, 1941.

The syphilitic distortions of the aortic valve and ring generally accepted as the causes of insufficiency and the usual explanations of their genesis are described and discussed briefly.

The study of a series of twenty-seven syphilitic hearts, including gradations from chronic to fulminating lesions, disclosed aortic valve distortions falling outside of those commonly described, which could not be accounted for by the generally accepted explanations of pathogenesis.

All of the valve distortions studied appeared to have been due to two processes: (a) a destructive inflammation of the aortic wall resulting in destruction and dislodgment of the cusp attachments at the commissures and (b) a reparative fibrosis.

These two processes, destructive inflammation and reparative fibrosis, are set forth and discussed as the basic factors in the genesis of aortic insufficiency due to syphilis. Reference is made to earlier brief statements to this effect by Mallory and Norris.

Support for the idea that destruction of tissue plays a significant part in the production of syphilitic valvular distortions is found in the partial reproduction of such distortions by dissection of normal valves.

AUTHOR.

Prado, A. De A.: Intrapericardial Aortic Aneurysm. *Rev. argent. de cardiología* 8: 105, 1941.

A case is reported of intrapericardial aortic aneurysm confirmed by autopsy; during life it presented a difficult problem of differential diagnosis from a diverticulum of the pericardium.

The great size of the paracardiac tumor, its faint pulsation, the angulated form of the radiological contour, and the long course of the malady may be found in both cases. Synchronism of the tumor pulsations with those of the aortic arch as shown by roentgenkymograms may be a sign of aneurysm of diagnostic value.

In cases of highly located intrapericardial aortic aneurysms, as the case reported, there is no typical syndrome which may distinguish them from extrapericardial aortic aneurysms, as Cossio and others hold. On the contrary, those of low, supra-valvular location, one case of which is briefly reported, have a typical syndrome.

AUTHOR.

Bohnengel, C.: Auriculo-Ventricular Heart Block With Stokes-Adams' Syndrome in a Patient With Syphilitic Heart Disease and Diffuse Myocarditis. *J. Indiana M. A.* 33: 617, 1940.

A case presenting clinical and post-mortem evidence of syphilitic heart disease with aortic insufficiency, cardiac enlargement, and congestive heart failure is reported. The illness was complicated by auriculoventricular heart block and Stokes-Adams' attacks. The patient died during an attack, and at autopsy a diffuse myocarditis was found in the interventricular septum. The combined clinical, laboratory, and au-

topsy findings point to syphilis as a possible etiologic agent for the production of the lesion and its accompanying disturbance in conduction, but conclusive proof is lacking.

AUTHOR.

Carr, F. B.: Heart Disease in Pregnancy. *M. Ann. District of Columbia* 10: 1, 1941.

In the first years following the establishment of the Prenatal Cardiac Clinic at the Boston Lying-In Hospital, there was a mortality rate of about 12 per cent among pregnant cardiac patients. This rate gradually fell, and in 1933 it was about 6.4 per cent; at the present time less than 3 per cent of all cardiac patients succumb to the dangers of pregnancy. It has been the experience at this hospital and also at the Worcester City Hospital, where a similar clinic has been existent for about ten years, that nearly half of this expressed mortality occurs in patients who have not attended the clinic but have been hastily referred to the hospital with the sudden onset of critical heart failure.

It is possible that with adequate prenatal care, which implies frequent and careful observation of the patient by the internist and the obstetrician, as well as implicit cooperation on the part of the patient, the mortality rate among pregnant cardiac patients might be gradually lowered, to finally approximate the fatality rate in everyday obstetrics. However, there are several barriers that appear insuperable now, such as subacute bacterial endocarditis, accounting for 0.8 per cent mortality, and fatal embolism, also accounting for 0.8 per cent. It is wishful thinking to believe the cardiac patient can be as good a risk as the normal woman. The astonishing and gratifying feature is how high a percentage of them can bear children and apparently be none the worse for it.

AUTHOR.

Browning, J. S., and Clark, C. J.: Paroxysmal Auricular Tachycardia Complicating Pregnancy. *J. Indiana M. A.* 34: 21, 1941.

Two cases of paroxysmal auricular tachycardia complicating pregnancy are reported.

The incidence of this condition in pregnancy is rare, occurring in less than 1 per cent of known cardiac patients and much less in otherwise normal persons. The history of previous attacks should warn of recurrence during pregnancy.

Paroxysmal auricular tachycardia usually occurs in otherwise normal hearts.

Quinidine is an effective drug in stopping attacks of paroxysmal auricular tachycardia and may be used in pregnancy without fear of precipitating premature labor.

Electrocardiographic evidence of myocardial damage is often unreliable, because it may represent merely cardiac fatigue.

AUTHORS.

Schroeder, H. A., and Steele, J. M.: Studies on "Essential" Hypertension: II. The Association of Hypertension With Organic Renal Disease. *Arch. Int. Med.* 68: 261, 1941.

Two hundred fifty cases of so-called essential hypertension have been studied with a view to ascertaining the presence of organic renal disease. One hundred seventy-eight have been studied especially as regards the genitourinary tract. Evidence of renal disease of a nature not usually considered to be dependent on hypertension has been found in 113 cases.

Organic renal disease is a common occurrence in cases of essential hypertension. Examination of the genitourinary tract for abnormalities is an important part of the study of cases of hypertension. A history of renal disease often antedates the onset of arterial hypertension, even when no abnormality can be found. There is justification for regarding the condition in these cases no longer as "essential" hypertension but a different disease.

AUTHORS.

Corcoran, A. C., and Page, I. H.: Renal Aspects of Experimental and Clinical Hypertension. J. Lab. & Clin. Med. 26: 1713, 1941.

This is a critical review of the recent publication describing the relationship between the changes in the kidney and hypertension. It is stated that the final origin of hypertension remains obscure, for the demonstration of the part played by the renal pressor system clarifies some aspects of its etiology but, at the same time, poses new problems.

MCCULLOCH.

Lamport, H.: Formulae for Afferent and Efferent Arteriolar Resistance in the Human Kidney: An Application to the Effects of Spinal Anesthesia. J. Clin. Investigation 20: 535, 1941.

The application of Poiseuille's law to the kidney has been discussed, and formulas have been developed to measure clinically, in man, afferent and efferent arteriolar resistance. A practical application to available clinical data on the renal effect of spinal anesthesia (denervation) in normal man has also been offered. At present, while normal man may lack tonic central nervous control of renal blood flow, this does not appear to have been demonstrated. The evidence also does not preclude autonomous control by the kidney of its blood supply.

Incidentally, empirical formulas for the viscosity of human plasma and whole blood have been derived from observations in the literature.

AUTHOR.

Lamport, H.: The Relative Changes in Afferent and Efferent Arteriolar Resistance in the Normal Human Kidney. J. Clin. Investigation 20: 545, 1941.

Formulas for the afferent and efferent arteriolar resistance to renal blood flow in man have been applied to available data for normal subjects under ischemic, basal, and hyperemic renal conditions.

It has been found that the resistance of both sets of arterioles vary simultaneously in maintaining constant glomerular filtration in the basal state and in ischemia and pyrogenic hyperemia of the human kidney.

At the mean basal state, a 1 per cent decrease in renal blood flow per unit diodrast tubular mass is caused by approximately a 0.2 per cent decrease in afferent arteriolar resistance and a 0.9 per cent increase in efferent arteriolar resistance.

The heat loss due to friction of the blood flowing through the efferent arterioles is not approximately constant.

AUTHOR.

Corcoran, A. C., Smith, H. W., and Page, I. H.: The Removal of Diodrast From Blood by the Dog's Explanted Kidney. Am. J. Physiol. 134: 333, 1941.

Diodrast intravenously infused in dogs is unequally distributed between the plasma and red blood cells, the distribution ratio between cell and plasma water being approximately 0.50.

At low renal loads the extraction of diodrast from arterial plasma during its passage through the explanted kidneys of dogs averaged 0.84. Diodrast extraction was not affected by uninephrectomy.

Renal extraction of diodrast from arterial red blood cells averaged 0.20.

The removal of diodrast from arterial blood by the dog's explanted kidney is such that at low renal loads the ratio $\frac{\text{plasma diodrast clearance}}{\text{renal plasma flow}}$ is approximately 0.87.

AUTHORS.

Friedman, B., Jarman, J., and Klemperer, P.: Sustained Hypertension Following Experimental Unilateral Renal Injuries. Effects of Nephrectomy. Am. J. Med. Sc. 202: 20, 1941.

Sustained hypertension was produced in rats by means of unilateral renal injury (perinephritis from enveloping the kidney in a cellophane envelope).

Hyalinized and necrotic vascular lesions were observed in some animals. Their presence was associated with rapidly rising severe hypertension but was not related to the duration of hypertension or to the presence of nitrogen retention.

Removal of the injured kidney from the hypertensive animals resulted in a decline in blood pressure, not to the prehypertensive level, but to some point above it depending upon the severity of the hypertension. Maintenance of an elevated pressure long after removal of the injured kidney suggests that irreversible changes have occurred which may or may not be related to the changes in the vessels.

AUTHORS.

Jeffers, W. A., Montgomery, H., and Burton, A. C.: Types of Orthostatic Hypotension and Their Treatment. Am. J. M. Sc. 202: 1, 1941.

The physiology of adaptation to the erect position is reviewed as the basis for an understanding of orthostatic hypotension.

The physiologic importance of peripheral vasomotor activity, plus changes in heart rate, is emphasized.

A clinical study of normal subjects, patients following sympathectomy, and those with orthostatic hypotension is reported, using chiefly the following criteria: blood pressure, pulse rate, digital blood flow, and skin temperature.

According to their reactions to the tests above, our patients have been classified as having orthostatic hypotension due to slight, or marked impairment of reflex vasomotor function, or to mechanical defects in the circulatory system.

These patients showed orthostatic hypotension in association with: lesions of the central and peripheral nervous systems (communicating hydrocephalus, tabes dorsalis, and nerve injury secondary to arterial occlusion), the post-infectious state, and venous angioma. In one patient no etiology could be discovered.

The clinical evaluation of patients with orthostatic hypotension is discussed and a rationale of treatment is outlined.

AUTHORS.

Galdston, M., Govons, S., Wortis, S. B., Steele, J. M., and Taylor, H. K.: Thrombosis in the Common, Internal and External Carotid Arteries. Arch. Int. Med. 67: 1162, 1941.

The case histories of two patients with right hemiplegia and mixed aphasia associated with thrombosis of the carotid arteries of the left side and sensitivity of the carotid sinus reflex of the other side are presented. The literature dealing with thrombosis of the carotid arteries is summarized.

Thrombosis of the carotid vessels was suspected because of the absence of arterial pulsations. The diagnosis was confirmed by study of cerebral arteriograms and encephalograms, surgical exploration and gross and microscopic examination of the specimens.

Careful examination of the arteries of the neck in all patients with hemiplegia, convulsive seizures, or syncope may lead to more frequent diagnosis of thrombosis of the carotid arteries. Often arteriography can be a diagnostic aid.

AUTHORS.

Sappington, S. W., and Horneff, J. A.: **Tibial Artery Changes in Comparison With Those of the Radial and Coronary Arteries.** *Am. J. Med. Sc.* 201: 862, 1941.

Tibial artery age period changes and arteriosclerotic changes short of occlusive lesions consist of the development of a progressively thickening intimal collar of split elastica and longitudinally arranged interwoven connective tissue, together with more frequent and more voluminous medial calcification. These changes are similar to those found in the radials, but are slightly greater for the intima and decidedly greater for the media. Medial calcification was about three times more common in the tibial than in the radial in this series. Atherosclerosis is seldom a feature of tibial artery change. Altogether the intimal thickening in the tibial as well as the radial is slight, especially as compared with the coronary, and seldom threatens the integrity of the lumen. As in the radial, the anatomic condition of the tibial artery has no inferential bearing on coronary sclerosis.

AUTHORS.

Deutsch, F., Ehrentheil, O., and Peirson, O.: **Capillary Studies in Raynaud's Disease.** *J. Lab. & Clin. Med.* 26: 1729, 1941.

In this investigation the capillary response was studied in twenty-nine cases of Raynaud's disease.

1. Capillaroscopic observation of cases of Raynaud's disease shows that the disease may be present before the appearance of the clinical symptoms. In these cases abnormal capillaries can be seen when other vasomotor symptoms are not present.

2. In the majority of cases of Raynaud's disease there exists a persistence of the subpapillary plexus and a persistent connection between it and the outgrowing capillaries.

3. Two objective measurements are introduced to test the dynamics of capillary circulation: (a) reflux time, i.e., that time which elapses before the capillary flow ceases, when the upper arm is compressed with a blood pressure cuff, pumped up to 30 mm. above the systolic blood pressure; (b) critical capillary pressure, i.e., that pressure at which the flow once again reappears when the cuff in the above experiment is gradually decompressed at the rate of 10 mm. per two seconds.

4. Capillaroscopy can define the severity of the disease more accurately than the gross clinical findings.

5. The preganglionic sympathectomy has a distinct influence on the capillary picture of Raynaud's disease: (a) in twelve of fourteen cases the speed of the blood flow increased; (b) in cases with a slow reflux time, the time increased, and vice versa; (c) in ten of fifteen cases the width of the capillaries decreased; (d) the capillary permeability decreased; (e) the dilatation of the excretory ducts of the sweat glands vanished after operation; (f) these changes in the capillary picture after sympathectomy become less distinct in time; (g) the subjective symptoms of the patient are to some extent independent of the clinical picture. Some have the

same typical capillary picture as before operation, even though relieved of complaints. Others show objective improvement clinically, but retain their subjective complaints, because a neurosis may become apparent, which may have been a part of the picture from the beginning.

AUTHORS.

Crouch, J. H.: Glomus Tumours: Clinical Picture and Physiology. *Canad. M. A. J.* 44: 356, 1941.

Certain interrelationships which exist between glomus tumors and the sympathetic nervous system are discussed briefly. They are especially evident in the symptoms of pain and sweating. It is believed that the neurological features are more important than the vascular ones.

AUTHOR.

Plewes, Burns: Multiple Glomus Tumours: Four in One Finger Tip. *Canad. M. A. J.* 44: 364, 1941.

A case of multiple glomus tumors on the finger is reported. There is no evidence that the multiplicity of tumors gives rise to any peculiarly different or more severe symptoms. It is suggested that the rare case of recurrence may have been of multiple glomus tumors, the secondary tumors being very small at the time of the first operation.

McCULLOCH.

Hertzman, A. B.: The Relative Responses of the Dorsal Metacarpal, Digital, and Terminal Skin Arteries of the Hand in Vasoconstrictor Reflexes. *Am. J. Physiol.* 134: 59, 1941.

The participation of the intermediate hand arteries, the dorsal metacarpal arteries, and the digital arteries, in the vasoconstrictor reflexes of the hand, has been studied by recording their volume pulses with the photoelectric plethysmograph.

These arteries do not usually participate in the so-called spontaneous waves (Figs. 1, 2, 6, and 7) or in the vasoconstrictor reflexes elicited by loud noises (Figs. 3 and 8), by immersion of opposite hand in ice water (Fig. 4), or by application of cold to the finger whose pad pulses are being recorded (Figs. 5 and 9).

These results are most simply explained by considering the vasomotor reflexes as highly selective with respect to the vascular topography involved in the reactions.

AUTHOR.

Hunter, W. C., Sneed, V. D., Robertson, T. D., and Snyder, G. A. C.: Thrombosis of the Deep Veins of the Leg: Its Clinical Significance as Exemplified in Three Hundred and Fifty-one Autopsies. *Arch. Int. Med.* 68: 1, 1941.

Thrombosis of the deep veins of the leg is appallingly frequent among middle-aged and older persons forced to bed for varying periods of time. The incidence in the present study was 52.7 per cent.

Bilateral involvement was found 110 times, and unilateral, seventy-five times. The right side alone was affected a little more often than was the left. Thrombi formed in the veins accompanying the larger arteries far more frequently than in other veins and were present in the soleus muscle more often than in the gastrocnemius.

Fatal pulmonary embolism was responsible for 3.13 per cent of all deaths; in 45.4 per cent of the cases of death from such embolism the most probable source was thrombosed leg veins. There is good authority for the belief that, although

fulminating emboli often spring from the femoral vessels, thrombosis here represents an extension from older clots in the legs and feet. From the standpoint of prophylaxis and treatment, recognition of this is most important.

Lesser emboli frequently originate from the veins of the calf. Showers of these, even though of small diameter, may consist of long clots, which, by buckling or coiling, are capable of occluding even the major pulmonary arteries. Repeated embolic episodes are more frequent than a single massive attack. Multiple small fragments can also do harm by placing an added burden on an already embarrassed circulatory system.

In the present series there was little difference in the incidence of thrombosis between medical and surgical patients or between males and females.

Phlebitis, either as a cause or as a complication of thrombosis, had a minor role in our cases.

As a rule, phlebothrombosis of the deep veins of the leg is clinically silent and for this reason is likely to be forgotten until embolic phenomena appear.

We are of the opinion that the greatest single factor favoring thrombus formation in the lower extremity is sudden confinement to bed of a previously ambulatory older person without the benefit of active exercise or the aid of gravity in the maintenance of an efficient venous circulation.

Planned and supervised voluntary movement and the elimination of too much comfort for the legs should do much to reduce incidence of thrombosis and its all too frequent sequel—pulmonary embolism.

AUTHORS.

McDowall, R. J. S.: *Problems of Circulation. The Oliver-Sharpey Lectures to the Royal College of Physicians of London.* Brit. M. J. 2: 39, 75, 1941.

A biographical sketch of George Oliver describing the state of physiology of the circulation in his time and the part played by Oliver in laying down foundations for further development of this science is presented. Oliver worked for a closer relationship between physiology and medicine.

McCULLOCH.

Turner, G. G.: *A Bullet in the Heart for Twenty-Three Years.* Surgery 9: 832, 1941.

The case of a man who is still alive and well and who has been going about his daily work for the last twenty-three years with a machine gun bullet lodged in the wall of the left ventricle is reported. It was possible to remove this foreign body at operation.

McCULLOCH.

Reynolds, Samuel R. M.: *Dermovascular Action of Estrogen, The Ovarian Follicular Hormone.* J. Invest. Dermat. 4: 7, 1941.

A review is given of the experiments reported in earlier papers on the vasodilating effect of estrogen on the capillaries and venules in the skin of the ear of the rabbit and in the human male. The increase in finger-volume involves the capillaries and venules, and does not alter appreciably the rate of blood flow through the skin. The response is in the same direction, though less than that seen in the genital tract following injection of estrogen.

A summary is made of work now in progress on the dermovascular effect of estrogen in women in menopause. It is shown that two types of response may occur, one, a sustained plateau, the other, a flush-type of response. The latter is observed in women who are nervous before treatment, or during a period of return

of symptoms in the course of treatment. The dermovascular effect of estrogen appears to become less marked as relief from vasomotor disturbances takes place.

Comparison is made of the menopausal flush and the dermovascular reaction to estrogen. It is shown that in both vasodilatation occurs, but that in the menopausal flush the effect is in part due to arteriolar dilatation, and in the estrogen response, the smallest vessels beyond the arterioles are concerned. The former involves intermediation of nervous activity (inhibition of arteriolar tone), the latter appears to be a direct effect of the hormone on tissues in or about the blood vessels.

AUTHOR.

Rubin, M. I., and Rapoport, M.: The Mode of Action of Magnesium Sulphate in Reducing the Hypertension of Acute Glomerulonephritis. *Am. J. M. Sc.* 201: 734, 1941.

In the patient with acute glomerulonephritis and hypertension, magnesium sulphate lowers the blood pressure without producing dehydration.

The intravenous administration of hypertonic sucrose produces diuresis, and generalized and cerebral dehydration, without lowering the blood pressure. Occasionally it elevates the blood pressure. The dangers of this secondary rise in blood pressure in the acute nephritic are pointed out.

Magnesium sulphate in the doses employed may be ineffectual in patients with large urinary volumes.

The mechanism by which magnesium sulphate reduces elevated blood pressure is discussed.

AUTHORS.

LeRoy, George V.: The Effectiveness of the Xanthine Drugs in the Treatment of Angina Pectoris. I. Aminophylline. *J. A. M. A.* 116: 921, 1941.

Sixty-eight patients with angina pectoris were given aminophylline or placebos in varying amounts over a period of two years. In general, aminophylline benefited 75 per cent of the sufferers. Placebos and sedative drugs were reported beneficial by about 20 per cent of the group. When patients who had been benefited by the use of aminophylline were given placebos or stopped taking the drug, about 80 per cent experienced a return of symptoms within less than three months.

AUTHOR.

Book Reviews

LA INSUFICIENCIA CARDIACA: By Dr. Cristián Cortés Lladó, Antiguo Jefe del Servicio de Cardiología de Cataluña. De la Escuela de Medicina de Barcelona. Compañía General Editora, S. A., Mexico, D. F., 1940, 186 pages, 30 illustrations, \$3.00.

This booklet, which was designed for general practitioners, deals with the general problem of congestive heart failure. It follows the classical pattern of the French School, from Beau to Vaquez, from Lian to Laubry.

The conception of isolated failure of either ventricle, and of the left auricle, is accepted.

In a few short chapters the author describes the contributions that radiology, electrocardiography, and measurement of cardiac output have made to the diagnosis of heart failure. In spite of the many interesting details, the conclusions reached in these chapters are not always convincing.

A large bibliography is included. However, there is no mention of many studies on heart failure which have been published in the last ten years, notably those of Luisada, Rigoni, Harrison, Fishberg, and Altschule. If these studies had been taken into account, some of the conclusions might have been modified.

In general, the book is evidence of the difficulty of writing for general practitioners a brief, but complete and modern, description of heart failure.

ALDO LUISADA.

INFLUENCE OF THE THYROID HORMONE ON HEART AND CIRCULATION: By Håkon Rasmussen, Institute of Physiology, University of Oslo. Acta med. Scandinav., Suppl. CXV, 1941; 202 pages, 12 figures, and 38 charts.

After an excellent review of the literature, this monograph is concerned with the author's prolonged investigations on twenty trained dogs, of which twelve were fed thyroid, three were given thyroxine, and five received dinitrocresol over a period of many months, unless interrupted by death.

Most of the animals which received thyroid or thyroxine did not seem unusually nervous, although all showed a marked increase in oxygen consumption. Tachycardia was regularly present early in the experiments, but, in the majority of instances, the heart rate later declined to a normal level, with intervals of tachycardia. Exercise tests resulted in abnormal tachycardia, so that instability of the heart rate, rather than constant tachycardia, was characteristic.

The systolic pressure rose, but the diastolic was little affected. The cardiac output (Fick method) was increased *pari passu* with the oxygen consumption, so that the average arteriovenous difference was unaltered. The electrocardiogram exhibited characteristic, but often temporary, changes; inversion of the T waves and an increase in the Q-T interval were the most constant alterations.

The dogs died in a state of circulatory insufficiency, ushered in by extreme tachycardia, with low cardiac output and diminishing blood pressure, but without congestive phenomena. The autopsies showed no characteristic changes in the heart or vessels which might explain either death or the circulatory effects; adrenal hypertrophy was the most constant abnormality.

Feeding vitamin B₁₂ in addition to thyroid, did not ameliorate the effects of the latter.

Dogs which were fed dinitro-v-cresol developed increases in oxygen consumption comparable to those in the thyroid group, but, in contrast, had fever and bradycardia.

The author concludes that the thyroid hormone has a primary, deleterious effect on the heart and circulation and that the final circulatory failure is not secondary to the increased cardiac work. The tachycardia, far from being a compensatory mechanism, is extremely detrimental.

This is the most extensive study of the effects of experimental hyperthyroidism on the circulation that has been reported. The material is well arranged, and the prose is clear. The author is interested in throwing light on human hyperthyroidism by the method of animal experiments, so that clinicians will find the monograph readable and interesting. Most of the results corroborate the view of the disease which is current in this country. The monograph is well up to the high standard which we have been led to expect from Scandinavian research.

ISAAC STARR.

CARDIAC CLASSICS. A COLLECTION OF CLASSIC WORKS ON THE HEART AND CIRCULATION, WITH COMPREHENSIVE BIBLIOGRAPHIC ACCOUNTS OF THE AUTHORS: By Fredrick A. Willius, M.D., Chief, Section of Cardiology, The Mayo Clinic, and Thomas E. Keys, M.A., Reference Librarian, The Mayo Clinic. The C. V. Mosby Co., St. Louis, 1941, 858 pages, \$10.00.

"Cardiac Classics" is introduced by a foreword from the pen of Donald C. Balfour. In his short communication Dr. Balfour writes, "In the appraisal of medical literature, students and practitioners are likely to overlook the writings of those who established the fundamentals upon which subsequent progress has been made. These epoch-making contributions are also evidence of the fact that in the study of disease thorough and accurate observation is the first requirement and supercedes other methods."

The authors have chosen papers quite in keeping with Dr. Balfour's suggestions. These original papers present the work of investigators who carried on research in spite of obstacles, and most of these investigations were hampered by an almost total lack of equipment. As one reads these essays and tries to visualize the effort and persistence necessary to achieve so much, the wonder is not that medical science lagged so long, but that it has achieved so much with resources so slender.

The first paper included in the series is the essay, "On the Motion of the Heart and Blood in Animals," which William Harvey presented in 1628; the last (save a poem by Oliver Wendell Holmes) is the paper by James B. Herrick on "The Clinical Features of Sudden Obstruction of the Coronary Arteries," published in 1912. In between are fascinating contributions. All of these are important in the history of cardiac disease; the progress of investigation in cardiac structure, function, and disease is portrayed in these original papers.

Each contribution is accompanied by a likeness of the author; many of these are copies of portraits. Also, a short biography is the preface to each essay, which adds much to the interest. Thus the reader has a glimpse of the social background, the status, and activities of the leading practitioners through several generations.

Fifty-two communications from fifty-one authors make up the collection. Among many original essays, one finds Malpighi's report "About the Lung," "Early Experiments on Blood Pressure and Blood Velocity," the work of Stephen Hales, Auenbrugger's essay on "Percussion of the Chest," and Withering's "Account of the Foxglove." A long chapter is given to Laennec's "Treatise on Mediate Auscultation." Corvisart, Caleb Parry, James Hope, Corrigan, Stokes, Duroziez, Potain,

Von Leeuwenhoek, Morgagni, Traube, Cohnheim, His, Jr., and many others who shared in the development of the knowledge of cardiac disease are represented in this collection.

The book is not devoted entirely to the pioneers of research who laid the foundations of the knowledge of cardiac disease and developed the facts of cardiac physiology and pathology slowly through two hundred years and more. Important communications of fundamental value of recent date and modern type are included. Einthoven's first presentation of the use of the string galvanometer in the electrocardiograph is included. Among the papers from the modern group are those by James Mackenzie, Walter Keith, and Broadbent. One very interesting lecture is that given in 1896 by Francis H. Williams on the use of the fluoroscope for determining the outline of the heart.

The reviewer agrees with the authors that "it is reasonable to conclude that the classics of medical antiquity form the basis of modern medicine and that the physician of today relinquishes many cultural advantages when he avoids the acquaintance with his distinguished predecessors."

The book is beautifully bound and well printed, and the numerous reproductions of portraits are satisfactory. To the physician who is interested in medical history, particularly if much of his work is with cardiac patients, this book will make an especial appeal; it can be heartily recommended to all physicians who find pleasure and instruction in the study of the achievements of the great men whose vision and industry laid a sure foundation.

JAMES G. CARR.

MANAGEMENT OF THE CARDIAC PATIENT: By William G. Leaman, M.D., Assistant Professor of Medicine in charge of the Department of Cardiology, Women's Medical College of Pennsylvania. The J. B. Lippincott Co., Philadelphia, 1940, 705 pages, 255 illustrations, \$6.50.

Those who believe that any book review worthy of the name must consist largely of adverse criticism need waste no time reading this one. To the present reviewer Dr. Leaman's book seems distinguished by many excellent qualities, and easily to be rated among the few good volumes devoted to treatment of the sick patient. It differs considerably from most textbooks on heart disease, as one would expect from its title. The author's aims are set forth clearly in the preface, where he modestly states that "this small volume attempts to assemble the facts that are most essential in the management of the cardiac patient," and he indicates further that it was written primarily for the guidance and help of the general practitioner.

It is not a particularly small volume, even in comparison with the supergigantic books that are the current fashion in medical texts. It contains about 650 pages, not counting eighteen pages of selected bibliography. After reading the entire book carefully, I find it difficult to believe that it could be reduced in size without materially impairing its value.

Emphasis is properly laid chiefly upon the details of treatment, but all modern methods of diagnosis are discussed in detail and their value appraised. Heart disease is classified according to etiology and functional capacity, rather than upon the basis of structural lesions. All the recognized etiologic types (rheumatic, syphilitic, hypertensive, etc.) are adequately considered, and, in addition, there are valuable chapters upon the heart in pregnancy, cardiac problems in surgical practice, cardiac emergencies, and the place of physiotherapy and of diet. Several of the author's colleagues who specialize in other fields have contributed chapters on the relation of allergy to the heart, the role of social service, and the various surgical measures now employed in the treatment of anginal pain, hypertension, effort syndrome, and suppurative pericarditis. There is an excellent section on electrocardiography, with more than 80 pages.

The author would probably be the first to insist that his book should be used as a supplement to other recognized texts, inasmuch as his chief interest is in treatment, whereas that of most "standard" texts is in diagnosis. But it is impossible to read this volume carefully without learning all the important diagnostic procedures and, in addition, far more about prognosis than is possible from books that do not include detailed case histories. The author's comments—wise, conservative, and lucidly stated—gain in cogency when made in connection with the diagnosis or treatment of a particular patient whose history and progress are recorded at some length. Even without case histories this would be an excellent volume for all practitioners who are entrusted with the care of cardiac patients, but the inclusion of such records adds greatly to its value. Some of these are necessarily brief, but many of them follow the course of patients for weeks, months, or even years, and display more clearly the variable responses to different therapeutic procedures than any other method could do. These do not follow any fixed pattern, but include the essentials; one of the most interesting and illuminating is presented in the form of a series of letters from a patient over a period of almost two years, with explanatory comments by the author.

Throughout the book one is impressed by the fact that Dr. Leaman writes of matters with which he has had long and intimate experience. His knowledge has obviously been derived not merely from careful reading of cardiovascular literature, or even from ward visits and the autopsy room, but also from the prolonged, day-to-day care of sick people in the hospital, office, and home. His discussions are marked by authority and wide knowledge of recent advances. The illustrations are superbly reproduced and add much to the value of the text. The author is to be congratulated upon having made a real contribution to the aspect of heart disease that seems to many of us the most important, but receives scant attention in most books.

H. M. MARVIN.

Correspondence

TO THE EDITOR:

In his article on the duration of electrical systole in massive pericardial effusion (AM. HEART J. 22: 35, 1941), Chen-Lang Tung states: "In the rather large literature of the electrocardiographic changes in pericardial effusion, no mention has been made as to the effect of such effusion on the Q-T duration." I wish to direct attention to the work of Dressler (*Klinische Elektrokardiografie*, 1937) and ter Horst (*Acta Med. Scand.* 101: 362, 1939), both of whom described an abnormal *shortening* of the Q-T interval in pericardial effusion which they claimed could be used as a diagnostic aid. The latter investigator included a case wherein the decreased Q-T returned to normal after adequate pericardiocentesis, but close scrutiny of the protocol reveals that the limitation of systole was merely relative, not absolute.

From a personal study of four patients with pericardial effusion, I am able to confirm Tung's statement that the Q-T interval is not significantly shortened. Incidentally, in one of the two cases in which electrocardiograms were taken before and after tapping on several occasions, the Q-T interval varied significantly in only a single instance.

The value of Tung's thesis is limited, however, by the fact that the Q-T interval is not abnormally lengthened in all cases of cardiac failure.

EDWARD SHAPIRO, M.D.
Beverly Hills, Calif.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. PAUL D. WHITE
President

DR. ROY W. SCOTT
Vice-President

DR. T. HOMER COFFEN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

*DR. EDGAR V. ALLEN	Rochester, Minn.	*DR. EDWIN P. MAYNARD, JR.	Brooklyn
DR. T. HOMER COFFEN	Portland, Ore.	*DR. THOMAS M. MCMILLAN	Philadelphia
DR. CLARENCE DE LA CHAPELLE	New York City	DR. JONATHAN MEAKINS	Montreal
DR. WILLIAM DOCK	San Francisco	DR. E. STERLING NICHOL	Miami
DR. HUGH FARRIS, St. John, N. B.,	Canada	DR. FRANKLIN R. NUZUM	Santa Barbara
DR. NORMAN E. FREEMAN	Philadelphia	*DR. STEWART R. ROBERTS	Atlanta
DR. GEORGE R. HERRMANN	Galveston	*DR. ROY W. SCOTT	Cleveland
DR. T. DUCKETT JONES	Boston	DR. FRED M. SMITH	Iowa City
*DR. WILLIAM J. KERR	San Francisco	*DR. HOWARD B. SPRAGUE	Boston
DR. EMANUEL LIBMAN	New York City	DR. WILLIAM D. STROUD	Philadelphia
DR. DREW LUTEN	St. Louis	*DR. PAUL D. WHITE	Boston
DR. GILBERT MARQUARDT	Chicago	DR. FRANK N. WILSON	Ann Arbor
*DR. H. M. MARVIN	New Haven	*DR. IRVING S. WRIGHT	New York City
		DR. WALLACE M. YATER	Washington, D. C.

DR. H. M. MARVIN, *Chairman, Executive Committee*
and Acting Executive Secretary

GERTRUDE P. WOOD, *Office Secretary*

TELEPHONE CIRCLE 5-8000

THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-seven physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$11.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

**Executive Committee.*

The American Heart Journal

VOL. 22

NOVEMBER, 1941

No. 5

Original Communications

PERNIO: A VASCULAR DISEASE

TERESA MCGOVERN, M.D., AND IRVING S. WRIGHT, M.D.,
WITH THE COLLABORATION OF ERICH KRUGER, M.D.,
NEW YORK, N. Y.

THE condition referred to in this paper as "pernio" may be effectively studied and treated by considering it as a distinct vascular syndrome. In the past, the nomenclature has included many variations and stages of this disease which the investigators have classified under fifteen or more names, including chilblains,¹ erythema induratum,² Bazin's disease,^{3, 4} erythrocyanosis,⁵⁻⁷ dermatitis hiemalis,⁸ l'engelure,⁹ lupus pernio,¹⁰⁻¹² pernio,¹³ Frostschaeden,¹⁴ erythrocyanosis crurum puellaris,¹⁵ and acrocyanosis.¹⁶

A review of the literature back to Bazin³ (1858) indicates the necessity for clarifying a confused picture. In American journals the majority of the descriptions which have appeared have been written from the dermatologist's point of view.^{17, 18}

REVIEW OF LITERATURE

This syndrome has been erroneously confused with the erythema induratum of Bazin in many cases reported in the literature. In Bazin's original monograph³ there are several case reports which fit our description, but they are labeled erythema induratum. We believe that this has been in part instrumental in producing the confusion which exists in this subject, and it has led us to attempt a clarification at this time.

Bazin's erythema induratum is a tuberculide lesion¹⁹ (the tubercle bacillus was unknown at the time he wrote, 1857). Tubercles, not merely giant cells, must be present if one is to make a diagnosis of true Bazin's disease. The presence of giant cells seems to be the criterion of some authorities in classifying cases such as ours as tuberculide, thus

From the Vascular Clinic of the New York Post-Graduate Medical School and Hospital, Columbia University, New York.

Presented at the Sixteenth Annual Meeting of the American Heart Association, New York, June 8, 1940.

Received for publication Aug. 5, 1940.

adding further to the confusion in calling pernio "erythema induratum." Actually, giant or multinucleated cells are often seen in long-standing inflammatory processes.

Translations of some of Bazin's descriptions of erythema induratum will illustrate similarities to our cases, but, in the light of present knowledge, we feel that certain of them are descriptions not of true erythema induratum, but of "pernio."

As reported in Bazin's case 1, a laundress, aged 20, was examined May 21, 1858. She had never had enlarged glands. One sister had a seropurulent eye discharge. At the age of 11 she had an abscess at the angle of the left jaw which persisted to the age of 20. Her menses were irregular, not abundant, and often stopped for three months. Six months before the examination (in November), she developed red plaques on the lower part of her right leg, and these plaques increased in size. Two months later she developed similar lesions on the left leg. There were irregular plaques, 5 to 6 cm. in diameter, on the internal malleolus, which were violaceous in color; these disappeared with pressure. Touching them gave one the impression of an induration under each plaque. There were several smaller points in addition to the main areas. There were elongated plaques on the anterior surface of the tibia which were indurated and violaceous red. On the right leg there was a large irregular plaque which was violaceous red, with some sensation of an indurated band on palpation. In addition, there were several individual areas with the same characteristics, namely, they were indurated, regular, superficial, and not painful to pressure. (Bazin felt that the above facts distinguished this from the other types of erythematous nodules.)

Bazin suggested, in 1861, that in his opinion the suppression of menstruation was significant in producing these lesions. He did not note a seasonal variation, but he reported that the illness dated from November, that the patient entered the hospital May 21, and that she left July 2. At that time the redness and induration were practically gone. None of her family had a similar condition. The lesions in this case were not painful and did not progress to ulceration, but they were in other ways quite typical of the lesions noted in pernio.

In Bazin's Case 16, he reported that the lesions appeared on the subject's hands, nose, and jaw, and that they disappeared in the summer.

In Bazin's Case 66, he reported a man, aged 20 years, with ulcers of the leg and nasal bone. (This may, or may not, fit into our classification.)

In Bazin's case 67, he reported a man, aged 27 years, who had ulcers of the internal and external malleoli of the right leg, toes, and the soles of both feet. He also had pulmonary tuberculosis and tuberculosis of the kidney. His death was caused by Bright's disease. (We mention the general pathology in this case because it raises a serious question

as to the true character of these lesions which, although they bear certain resemblances to pernio, we feel were more likely tuberculous.)

In Bazin's case 146, he described a condition of chilblains in young females, particularly laundresses. In these cases the lesions had a predilection for the external and inferior portion of the leg and the surface along the Achilles tendon. It appeared that, at times, this condition was related to scrofula, but Bazin did not establish its connection with tuberculides.

It would appear from these descriptions that Bazin was dealing with two or possibly three different conditions, calling them "scrofula," when in reality, they were probably erythema induratum, tuberculosis, and pernio. Although there are no pathologic descriptions to confirm our impression, the clinical history in these cases tends to bear this out.

In 1894, Corlett²⁰ described pernio, which he called "dermatitis hiemalis," in a paper which was read before the Congress of Medicine in Rome. This deserves attention because it was the first attempt to discuss many of the characteristics of this syndrome. The following is a brief synopsis of his description of the disease. It is characterized by:

- (1) The sudden appearance of lesions at the first approach of cold weather;
- (2) Spontaneous cure in the spring;
- (3) The possibility that the condition may recur perennially for several years;
- (4) A characteristic appearance of the lesions on the dorsal surface of the hands most frequently, and on the corresponding surface of the feet next in frequency;
- (5) The fact that there is little or no tendency of the disease to spread to other parts of the body or to extend at the periphery after the lesions are fully developed;
- (6) The fact that "the eruption is characterized by vari-sized round or, as involution proceeds, horseshoe-shaped patches which are slightly raised, sometimes markedly thickened, and which have an abrupt, well-defined margin and a dusky-red or slightly erythematous color. At first, vesicles are present and rupture, leaving denuded, weeping, irregular pin-head to lentil-sized surfaces whose color is perceptibly stronger than the surrounding patch, and may be likened to a raw ham tint. Later, the patches take on a faded rose-colored hue, and they become covered with a thin layer of adherent scales";
- (7) The fact that the intensity of the violaceous color of the affected area varies with the temperature of the room and with elevation or depression of the hand;
- (8) The fact that itching may or may not be present;
- (9) The fact that the condition described is not associated with any other disease.

In 1896, Corlett²¹ again read a paper on this disease at the Third International Congress of Dermatology. In this paper there was little new except that he reported a difference in the size of the lesions under discussion. He reported fifteen cases, all of which occurred in cold weather, showed obstinacy to treatment, and invariably disappeared with the approach of warm weather. From this evidence it is certain that he was describing a type of disease which was dependent upon the presence of cold weather. Although this condition appears to resemble in some respects winter eczema of the type recently redescribed by Niles,²² it may easily have been a stage of development of pernio.

We believe that the confusion of the three conditions, pernio, erythrocyanosis, and the blue limb in anterior poliomyelitis, led Telford,²³ in his report of 1933, to arrive at the conclusion that Bazin's disease is no different from erythrocyanosis, that is to say, pernio. He seemed to base his conclusion on the presence of giant cells in the nodules. These, he contended, were the reason for calling the lesions tuberculous. However, no true tubercles were found. In this discussion it must be remembered that, at the time of Bazin, the tubercle bacillus had not yet been discovered, and that he did not include histologic descriptions of the lesions. The clinical histories, physical findings, and pathologic descriptions, as reported by Telford, are similar to ours.

Telford inferred that the lesions occurred only where there was an excessive deposit of fat, particularly in stout, florid people with large limbs. He held that a defective venous return, plus the excessive fat and the action of cold weather, combined to precipitate the lesions; that the clinical and histologic picture in this syndrome was identical with that of the purple limbs and chilblains of long-standing, severe poliomyelitis; that erythrocyanosis was identical with Bazin's disease; and that there was a common basis for all of these various lesions.

Eugman,²⁴ in 1919, described lesions almost identical to those which we will present, but he made no mention of their seasonal occurrence. He classified the lesions as tuberculides, and he spoke of their frequent occurrence in young girls working in the large shoe factories of St. Louis.

Klingmuller and Dittrich,¹⁴ in 1926, published a study on "Frost-schaden," and stated that the vascular damage in this condition leads to perniosis. Microscopic examination of sections revealed that there was secondary damage to the tissues, resulting from the initial damage to the vessels. This damage then extended into the fat tissues and the subcutis. The variations in the clinical picture depended upon the area involved, and varied from an elephantiasis-like swelling of the extremities in the fleshy areas to frank ulcers in the areas where the skin was thin. The ulcers appeared in the fall and winter.

Nardelli,¹³ in 1926, differentiated perniosis from Bazin's disease and stated definitely that the mere presence of giant cells was no reason for

classifying perniosis as a tuberculide. Rather, the presence of giant cells was evidence of cell destruction. He noted that perniosis had a seasonal occurrence, whereas true Bazin's disease did not. It was his opinion that the two conditions could coexist, but that tuberculosis was a complication rather than a cause of perniosis.

Von Norden,²⁵ in 1928, reviewed the literature and discussed the methods then in use for the treatment of perniosis. He reported the use of an ointment of salicylic acid, methyl ester, and oleum fali vale, or this product in conjunction with urea, for soaks or foot baths. According to von Norden, this treatment led to recovery in many instances. By recovery he meant not only the disappearance of the chilblains during the same winter, but also a reasonable assurance that the lesions would not recur the following winter.

Dittrich,²⁶ in 1929, attempted the correlation of the histologic changes with the clinical observations and commented on the multiform manifestations of perniosis folliculosis, due to the variations of the lesions of the follicles from slight edema to atrophy, associated with marked discoloration. He called attention to the hyperkeratosis of the follicles. No local anesthesia was used when taking the biopsies in his cases, so that changes in the skin could not be attributed to the effects of an anesthetic.

He concluded that ulcerative perniosis developed from the above histologic picture, with edema as the basic factor, and passed through the stage of bulla formation. The primary histologic defect occurred in the epithelium and the subepithelial layer. The ulcers showed the characteristics of necrosis, and tended, therefore, to mask the true lesion as described above. The area of predilection in one of his cases was the arms, and, in another, the ear; all the rest were confined to the lower portion of the legs. The ages of his patients ranged from 18 to 32 years.

Dittrich wrote as follows: "Chilblains or perniosis does not represent a 'freezing to death' of the tissues. Such severe damages are not necessary; rather, slight effects, either of repeated or chronic stimuli, are sufficient to produce this syndrome. It is not the frost, as such, but the variations in temperature which produce the stimuli. These stimuli represent a strain to the peripheral regulatory temperature mechanism, and particularly to the anatomical structures of this functional mechanism in the vessels of the skin, which are not capable of compensating properly for these demands because of a primary hereditary or acquired functional deficiency."

He preferred the name "perniosis" as an all-inclusive term, embracing all the stages of this disease. The etiology was still unknown, but it was definitely not tuberculosis. The tubercle bacillus was never found, either within frost-damaged tissue, or in guinea pig inoculations from this tissue. Of the multiplicity of precipitating factors, only one

remained constant, namely, lowering of temperature. He divided the disease into four stages similar to the classification suggested later by Buerger, and recounted below.

Dittrich's two articles are most comprehensive, and are worthy of study by all interested in this subject.

Perutz,¹⁵ in 1929, reported eighty cases of frostbite localized at the inner aspect of the knee joints. In his series, the disease occurred in girls and women only. This form of frostbite was not mentioned in the extensive paper on frost damages by Dittrich.²⁶ The age, sex, and good state of nutrition caused Perutz to call it "erythrocyanosis crurum puellaris." According to his description, the dermatosis appeared alone, or in combination with erythrocyanosis crurum puellaris. The slightest form was an erythema, varying in color from bright pink to dark red. The peculiar, icy coldness of the diseased skin was characteristic. The lesion differed from erythrocyanosis in the lack of violet discoloration. He divided the disease into four stages: color change, swelling of follicles, formation of small, livid nodules like those seen in perniosis, and, lastly, ulceration of nodules.

Perutz did not call it a new disease, but thought it was related to perniosis. Had he presented histologic material, we would be in a position to comment further. As it is, it should be pointed out that the stages, as he described them, are similar and comparable to what we shall describe, and that he probably was dealing with perniosis. The predilection for the knee joints and no other portion of the legs is difficult to explain. He mentioned that some authors believed erythrocyanosis was a superficial and diffuse form of tuberculosis of the skin, or a disease which was related to tuberculosis. He investigated these phases of the subject and was unable to correlate the clinical and dermatologic features with tuberculosis. This, too, has been our experience.

The endocrinologic background which was proposed by Perutz for this syndrome was based on the assumption of a vasoparalytic frost damage, superimposed upon an endocrine dysfunction of the capillaries. Since it is difficult to present the pros and cons of this view, and since such a discussion would only add to the confusion of the subject, it seems wiser to leave this matter in its present state of flux.

Lewis,²⁷ in 1929, mentioned a condition similar to ours, and called it "chilblains" or "erythema pernio," ascribing it to poor peripheral circulation or an injured vasomotor mechanism.

Kreindler and Elias,¹⁶ in 1931, described a juvenile acrocyanosis in young adults which they believed to be due to an endocrine disturbance or an imbalance in the autonomic nervous system, resulting in impaired circulation. The capillaries showed a spastic tendency, or a slowing of circulation, with dilatation of the venous branches and the venous subcapillary plexus. They stated that the reflexes of the larger vessels

were not changed, and that the disease followed a chronic course, becoming aggravated during cold weather and improving during warm weather. They made the interesting observation that there was spontaneous recovery in girls after marriage and in boys after they became 20 to 22 years old. This has not been true in our patients.

Fischl,²⁸ in 1931, suggested that more care be used in applying names to certain papulonecrotic lesions, in order to forestall confusion. Particular care should be taken in those conditions of uncertain etiology which have a resemblance to tuberculosis, but in which a relationship never has been proved. It would appear, from this paper, that among other conditions he probably had perniosis in mind.

Mayer and Cajkovac,^{29, 30} in 1932, described the seasonal variation in nonspecific sensitivity of the skin in eczema and related diseases. The peak was said to appear both in the spring and in the fall in the eczematous patients, as well as in the patients with lichen vivae and prurigo hebrae. Whether they had cases of pernio mixed with these groups it is difficult to say, since, as mentioned above, pernio of the hands was first described by Corlett,⁸ in 1891, and called "eczema." Most dermatologists of that period considered it an eczema.

Sannicandro,³¹ in 1932, described a case of a 60-year-old man with a skin lesion which took on the character of efflorescences that presented some of the histologic features of pernio; but here the distribution was more extensive than in many of the cases we have seen, and no seasonal variation was mentioned.

Buerger,³² in 1937, subdivided this condition (pernio) into four stages: (1) perniosis folliculosis; (2) infiltrating pernio; (3) bulbous stage; and (4) ulcerated form.

Knight,³³ in 1938, outlined a form of treatment for erythrocyanosis frigida. However, he merely made the statement that Bazin's disease, erythema induratum, affected girls, and elucidated no further.

During the past six years we have had the opportunity of studying ten patients with this disfiguring condition. It is fairly common in the North Temperate Zone, and occurs predominantly among women. Careful analysis shows that all patients suffering from this syndrome have a similar history. They present essentially the same clinical features and pathologic changes. Detailed reports of four typical cases will serve to illustrate our observations.

CASE REPORTS

CASE 1.—L. H., a woman, aged 29 years, was first admitted April 10, 1933. She was born May 18, 1903, in the United States. The family history was negative except that a brother had died of malignant hypertension. She had had hypertension for eleven years. Her first pregnancy had resulted in a miscarriage at five and one-half months because of toxemia and hypertension. The second and third children were stillborn at full term, in 1928 and 1929. In 1930, a fourth pregnancy was terminated in the sixth month by cesarean section because of a kidney complication. She had suffered from sore throats almost continuously until ten years before ad-

mission. The patient had never had edema, nocturia, or hematuria, but had had frequent throbbing headaches, with vertigo, nausea, and vomiting. She stated that she had complained of "growing pains" and rheumatic pains every winter since the age of 10 years.

Since the age of 7 years she had developed ulcers on her legs annually. These had occurred with the onset of cold weather in the fall, and had persisted until warm weather returned. Numerous small ulcers appeared simultaneously. Many of the ulcers had begun around the internal malleoli and gradually extended up to the calves. When they healed, they left a violaceous discoloration which would never disappear completely. It was in these areas that succeeding ulcers would form during the next cool spell. This condition was diagnosed as tuberculosis of the skin. She was given "gold injections," apparently with slight temporary improvement. Her feet became extremely white and painful when slightly chilled, but her hands never showed the same sensitivity to cold. During the months when the ulcers were open she had a low-grade fever at night, associated with drenching sweats, resulting in an annual winter weight loss of 30 to 40 pounds (one-fourth to one-third her normal body weight).

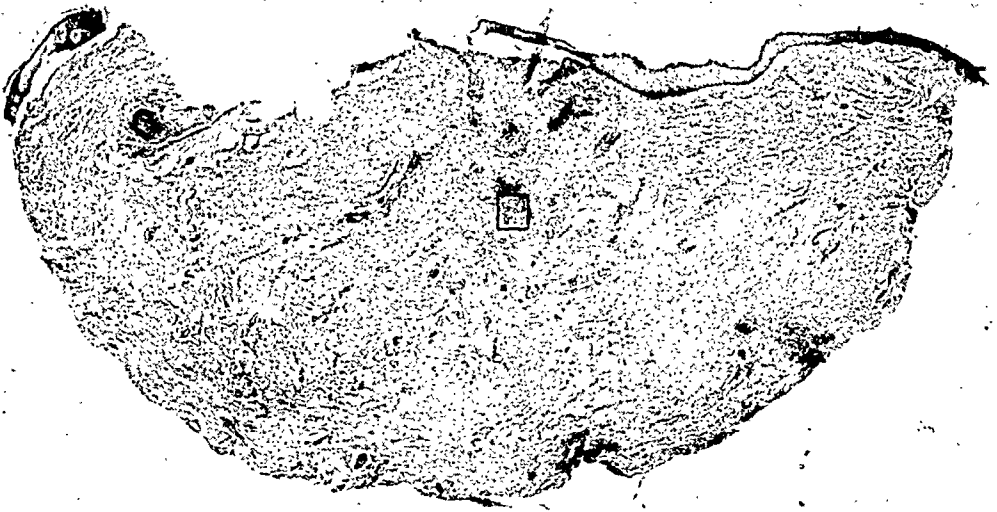


Fig. 1.—Case 1. Photomicrograph ($\times 40$) of lesion. Note prominent blood vessels in corium and necrosis in corium.

The physical examination on April 10, 1933, revealed that the tonsils were buried and that there was a profuse posterior nasal discharge. The teeth were carious; the gums were infected and bled easily. There were a few slightly enlarged cervical glands which were not tender, and a similar group of glands was present in the right axillary region. The lungs were essentially normal. The heart was found to be enlarged to the left. There was a systolic thrill and a prolonged systolic murmur over the mitral area. The pulmonic second sound was accentuated, and was louder than the aortic second. The blood pressure was 220/120. There were twenty to thirty reddened, indurated, tender, broken-down, nondischarging ulcers scattered bilaterally over the legs. Many superficial atrophic scars of small healed lesions were distributed through the same areas. The left radial artery was not palpable; the dorsales pedium were not palpable, and there was marked dependent cyanosis. No oscillometric readings could be made because of the presence of the ulcers.

Laboratory examination revealed no evidence of tuberculosis in the lungs, although, roentgenographically, there was evidence of an old, puerile, tuberculous focus at the hilus, and the Mantoux reaction was positive at a 1:1,000 dilution. She had an

aortic type heart. The electrocardiogram was normal. The basal metabolic rate was plus 4. The blood Wassermann reaction was negative. The erythrocyte count was 4,600,000, and the leucocyte count, 7,650. The hemoglobin was 11.46 Gm. (79 per cent), and the color index, 0.86. The differential leucocyte count showed polymorphonucleurs, 76 per cent; eosinophiles, 1 per cent; monocytes, 3 per cent, small lymphocytes, 6 per cent; and large lymphocytes, 14 per cent. Repeated urine examinations were negative except for a trace of albumin and an occasional hyaline cast. Chemical examination of the blood revealed nonprotein nitrogen, 37.2 to 39.8 mg.; urea nitrogen, 14.6 to 15.5 mg.; cholesterol, 470 mg.; and sugar, 107 mg., per 100 ml. blood.



Fig. 2.—Case 1. Photomicrograph ($\times 180$), enlargement of box in Fig. 1. Note small vessels surrounded by cuffs of polymorphonuclear and small mononuclear cells. Endothelial proliferation. Multinucleated cells are present but difficult to make out in this plate.

Biopsy of a lesion showed no evidence of tuberculosis. There was the usual cornification of squamous epithelium, without any evidence of hyperkeratosis or acanthosis. The corium contained many prominent blood vessels which were surrounded by small cuffs of polymorphonuclear and small mononuclear cells, as well as young, spindle-shaped fibroblasts. The vessels were also unusual in that they almost invariably showed endothelial proliferation, with occasional cells in mitotic division. Clusters of newly proliferated vessels suggested newly formed granulation tissue. There was some necrosis in the corium, with considerable recent hemorrhage, and there was also some evidence of fibroblastic proliferation, as well as a rare multinucleated cell. The process was a chronic, necrotizing one, in which healing by organization was prominent. The vascular reaction was the most conspicuous feature.

CASE 2.—A. H., a woman, 19 years of age, was first admitted April 5, 1938. She was born in the United States. The family history and past history were irrelevant.

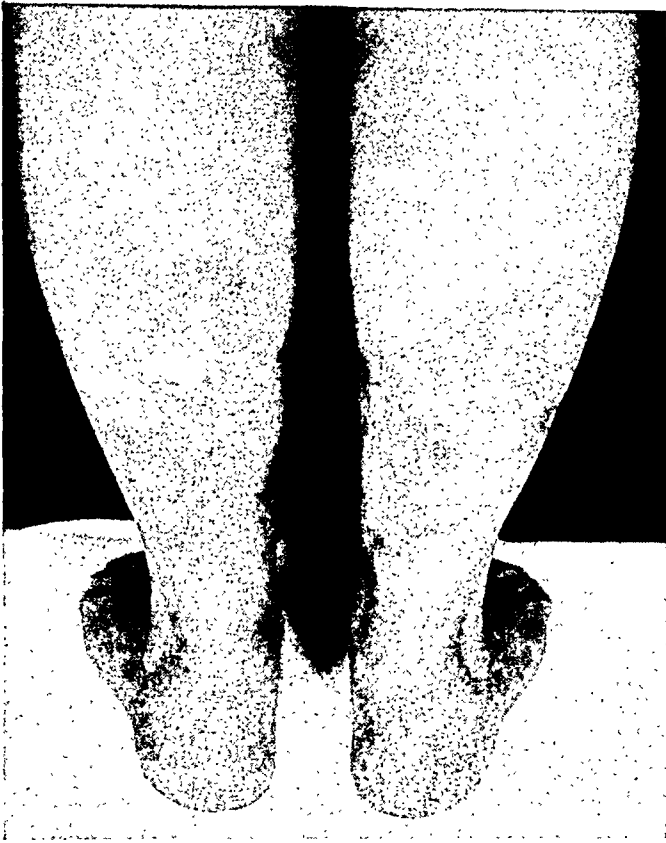


Fig. 3.—Case 2. Leg lesions. Posterior aspect. Note ulcer and pigmentation.

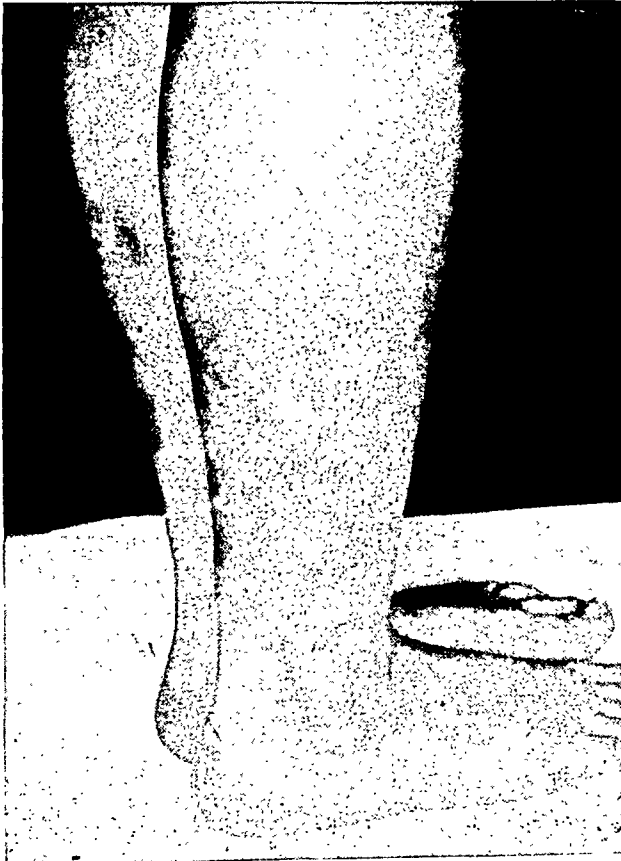


Fig. 4.—Case 2. Leg lesions. Lateral aspect. Note small ulcer above malleolus of right leg, and small ulcer on left leg, also pigmentation.

Following an injury to her right leg in March, 1937, the patient had noticed red blotches which were elevated above the surrounding surface. They had first appeared on the posterior surface of the lower third of the right leg. The lesions became more raised and scaly, and then appeared to come to a head, to ulcerate, and to heal. After two weeks in bed she still had the red blotches. The same type of lesion soon appeared on the left leg. During the summer of 1937 the lesions healed. However, in November, 1937, although there was no new injury to the leg, several lesions of the same type again appeared, each one developing into an ulcer. No treatment was instituted. In the late spring (May, 1938), all the lesions disappeared. There was a slight injury to the right leg about Christmas, 1938, when the condition returned and both legs ulcerated as previously. When seen late in the summer of 1939, the lesions had not completely healed, but were definitely improved and were confined to the lower third of both legs, along the medial and posterior surfaces. As in the other cases, when the lesions began to appear they were excruciatingly painful, but, after they ulcerated, the pain was less acute.



Fig. 5.—Case 2. Medical aspect of right leg, showing marked pigmentation and healing ulcers.

Physical examination on April 5, 1938, showed nothing abnormal except the leg lesions. Her blood pressure was 100/50, and the oscillometric readings were normal, as were the capillary studies. Roentgenologic examination of the lungs revealed nothing abnormal. The basal metabolic rate was plus 4; the Mantoux reaction was positive at 1:1,000; and the blood Wassermann reaction was negative. The erythrocyte count was 4,380,000, the leucocyte count, 8,000, the hemoglobin, 11.6 Gm. (70 per cent), the color index, 0.86, and the platelet count, 270,000. The



Fig. 6.—Case 2. Photomicrograph (×28) of lesion. Note small zone of ulceration.

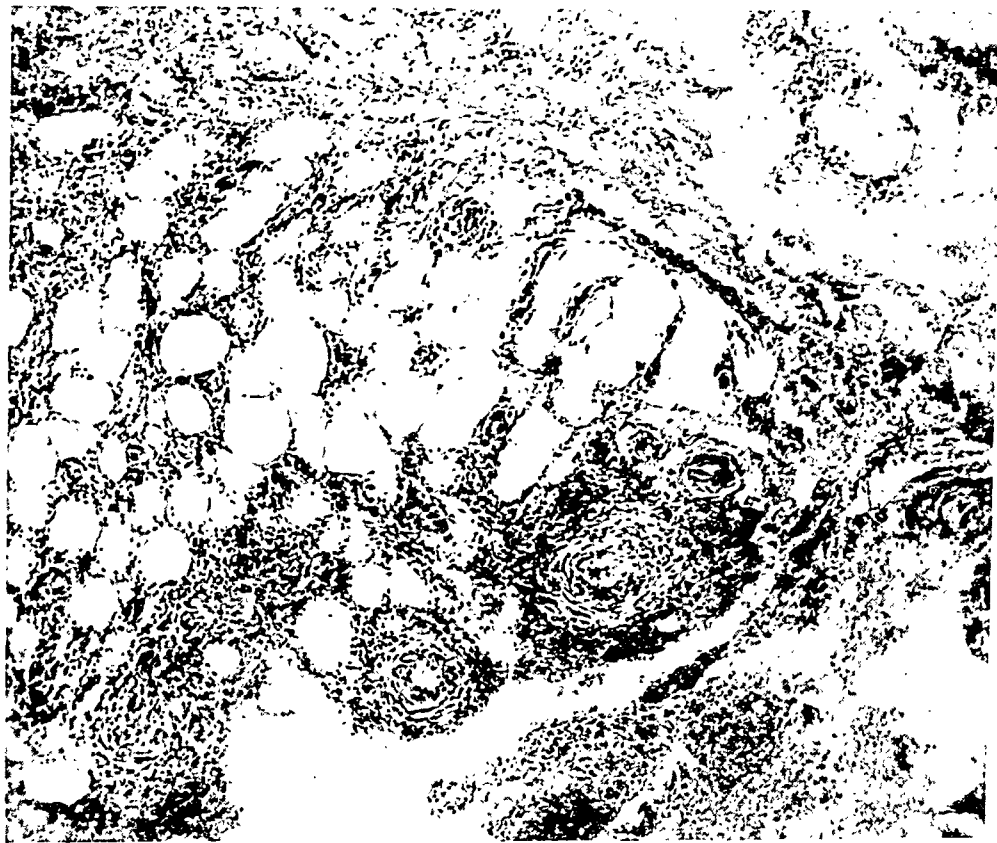


Fig. 7.—Case 2. Photomicrograph (×180), enlargement of box in Fig. 6. Panniculus is extensively necrotic, capillaries unusually prominent. Leucocytes as well as small lymphocytes infiltrate the adipose tissue. Note endothelial thickening and perivascular ring of fibrous tissue.

differential leucocyte count showed polymorphonuclears, 70 per cent; eosinophiles, 1 per cent; monocytes, 1 per cent; small lymphocytes, 26 per cent; and large lymphocytes, 2 per cent. A routine urine examination was negative, and the results of the Mosenthal two-hour renal function test were normal. Chemical examination of the blood revealed nonprotein nitrogen, 24 mg.; urea nitrogen, 10 mg.; and calcium, 9.3 mg., per 100 ml. serum. Ascorbic acid studies indicated the following: fasting blood content, 0.54 mg. per 100 ml. of plasma; saturation test,¹⁹ 355 mg. excreted in the twenty-four hours following injection of 1,000 mg.

Biopsy of a lesion revealed no evidence of tuberculosis. Except for a small zone of ulceration, the overlying squamous epithelium was not abnormal. Immediately beneath the basal cell layer there was an extensive leucocytic cellular reaction which was diffusely infiltrating the subcutis. The capillaries of this region were unusually prominent as a result of endothelial and pericapillary fibroblastic proliferation. The panniculus was extensively necrotic, containing many nuclear fragments, but showing no true caseation. Polymorphonuclears, as well as small lymphocytes, infiltrated the adipose tissue, and there was considerable fibrosis. The most conspicuous feature in the panniculus was the vascular change, which consisted of a chronic angiitis. Not only was the endothelium greatly thickened, but there was also a striking perivascular ring of fibrous tissue containing many cells, chiefly of the lymphocytic series.



Fig. 8.—Case 3. Anterior aspect. Ulcer over right internal malleolus and over dorsum of foot. Extensive pigmentation of both legs.

CASE 3.—O. H., a woman, aged 39 years, was first admitted Sept. 19, 1938. The family history was negative. The past history was not significant, except that in October, 1937, she had developed an eczematous condition involving the flexor surfaces of the legs, back, and hands, in that sequence. Roentgen therapy had been given. The condition had cleared up in ten weeks; its etiology was unknown.

At the age of 14 years the patient had developed red, indurated areas, which caused pain on pressure, on the inner and posterior surfaces of both legs. These had become inflamed and then had healed without ulceration, followed by complete disappearance of the lesions. The patient had had a similar attack in the fall of her eighteenth year, but for the first time the indurated, raised areas had become ulcerated. For the next seven years the legs were perfectly normal. At the age of 25 years the lesions had recurred after she had gone swimming late in the summer. The condition of her legs was such that she had remained in bed most of the time from October until June, wearing a gelatine boot which was changed at frequent intervals. The legs healed, and she remained well for three years. From her twenty-eighth year to the time of examination, a period of eleven years, her right leg had never completely healed, although it was definitely improved during the warm months of the year. The left leg had been free of ulceration for four years.



Fig. 9.—Case 3. Lateral aspect. Extensive pigmentation of left leg. Right leg has ulcers over dorsum and below external malleolus, and marked sclerodermic changes.

In October, 1938, she had excruciating pain across the right instep, and ulcers appeared between three toes of the right foot. Ulcers then appeared over the dorsum of the foot, and a single, large lesion persisted in this area. The pain in the reddened areas was knifelike in character. The areas were discrete and changed from red to violaceous in color. When the patient opened these lesions with a needle, a dark red serum exuded for a day, then a yellowish serum oozed out, and the lesions thereafter began to ulcerate, with cessation of pain. The ulcers took from four to five weeks to heal. The healed areas were deeply pigmented. On these pigmented areas the next year's crop of lesions became engrafted. The lesions were

open almost all winter (1938-1939), and the patient was confined to the house from October until the end of February.

Physical examination revealed nothing abnormal except the lesions on the legs. The skin was deeply pigmented and sclerodermic from the knees downward. A large, ulcerated lesion was present over the internal malleolus, and another over the dorsum of the right foot. The left leg merely showed the pigmentation, scleroderma, and evidence of healed ulcers. The oscillometric readings were normal.

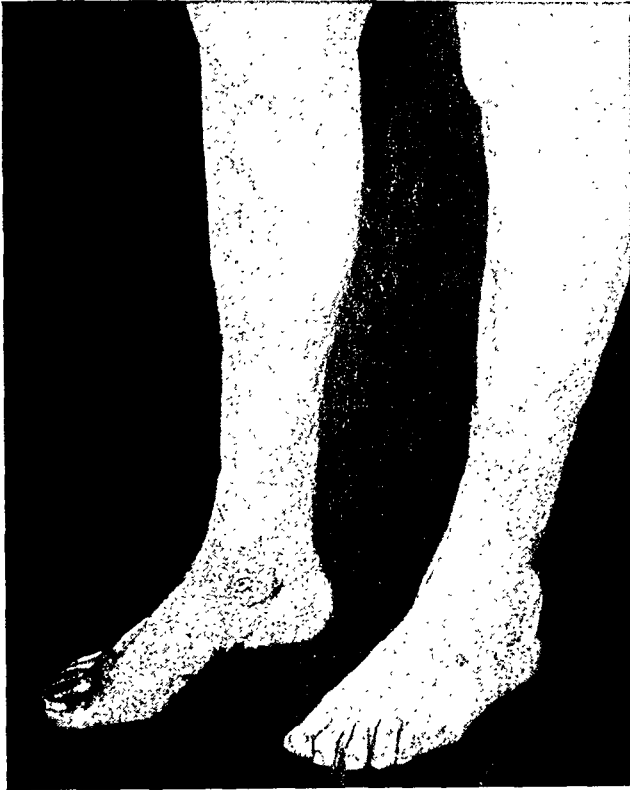


Fig. 10.—Case 3. Medial aspect, right leg and foot. Ulcer over internal malleolus. Marked pigmentation.

A roentgenogram of the lungs showed an old, inactive tuberculous focus in the right hilus, as well as an old Ghon node.

The sputum contained no tubercle bacilli; the basal metabolic rate was minus 15 per cent; the Mantoux reaction was positive at 1:1,000. The blood Wassermann reaction was negative. The erythrocyte count was 3,970,000; the leucocyte count, 5,000; the hemoglobin, 78 per cent; and the color index, 0.98. The differential leucocyte count showed polymorphonuclears, 68 per cent; eosinophiles, 2 per cent; small lymphocytes, 21 per cent; and large lymphocytes, 8 per cent. The urine examination was negative. Chemical examination of the blood showed that the urea nitrogen was 10 mg.; the uric acid, 3.7 mg.; the chlorides, 485 mg.; and the true glucose, 85 mg., per 100 ml. of blood. The sedimentation rate, by the Westergren method, was 18 mm. in 60 minutes.

Biopsy of a lesion showed no evidence of tuberculosis. There were an extreme degree of hyperkeratosis and a fairly large abscess within the squamous epithelial layer. It was apparent that this represented a chronic process of long standing, in which ulceration undoubtedly played a conspicuous role. This was indicated by the fact that nests of epithelium lay in isolated foci in the subcutaneous connective tissue. In this case, the angiitic reaction in the subcutis was a conspicuous feature.



Fig. 11.—Case 3. Photomicrograph (×50) of lesion. Note hyperkeratosis and abscess.

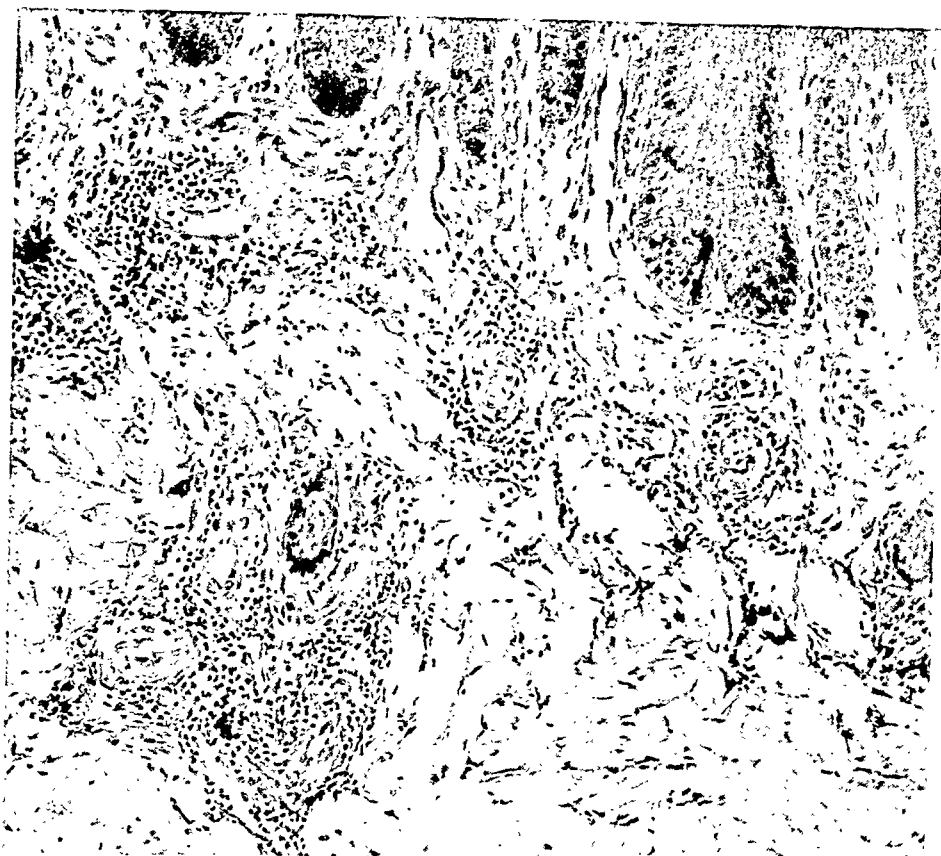


Fig. 12.—Case 3. Photomicrograph (×240), enlargement of box in Fig. 11. Nest of epithelium in the subcutaneous connective tissue. Vessel walls are greatly thickened with almost obliteration of lumina. Mitotic figures present but difficult to see in plate.

The vessel walls were greatly thickened, which had in some cases led to almost complete occlusion of the lumina. Each of the vessels thus involved was also surrounded by collections of neutrophilic leucocytes, lymphocytes, and large mononuclear cells. There was an extreme degree of necrosis in the panniculus adiposus. Some of the necrosis even suggested caseation. The chronicity of the condition was indicated by the extensive granulation tissue on the margins of the necrosis. An

interesting feature of the microscopic appearance was the presence of many cells in division, both in affected vessels and in the dermis.

CASE 4.—R. P., a woman, aged 39, was first admitted Feb. 7, 1939. She was born in Italy. Her family and past history were irrelevant. She had had two miscarriages and one full-term delivery, the latter in 1929.



Fig. 13.—Case 4. Ulcers over external and internal malleoli, dorsum of right foot, and between toes.

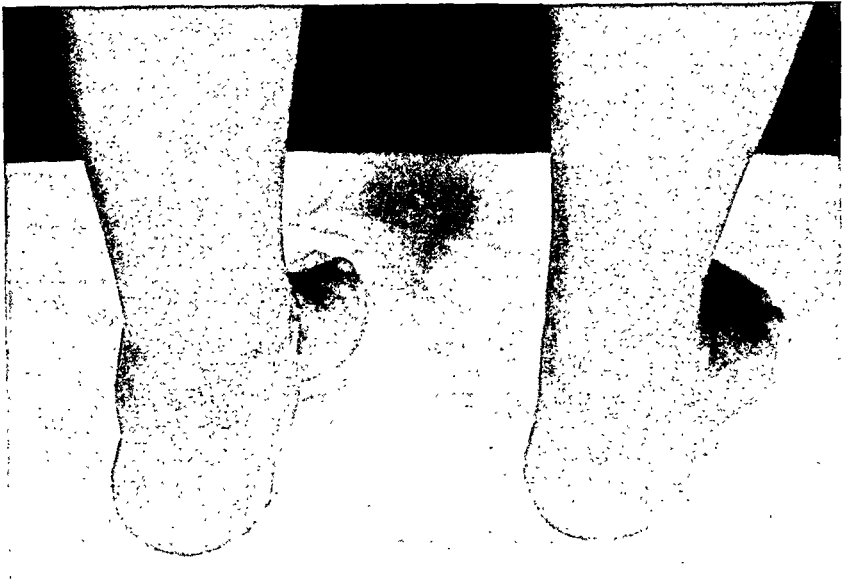


Fig. 14.—Case 4. Lesion in region of tendon Achilles.

In September, five years before, the patient first began to complain of cold, itchy feet. This was followed very shortly by blistering, with ulceration of the inner surface of the left ankle. Each summer the lesions would heal, but they appeared again each fall. The ulcers were treated with salves during this period in a skin clinic.

Whenever the patient was exposed to cold, she would have a burning feeling, followed by itching which was a sign of the initiation of the leg lesions. The areas would become bluish-red, and some even looked like subcutaneous hemorrhages. The lesions would vary in size from a petechial spot to a dime. Severe, knifelike pain which was worse at night was felt in the discolored areas. After two days to three weeks of this discomfort, a blister would form, exuding a pinkish or yellowish odorless exudate, followed by ulceration. A scab would form and the lesion heal. If at this stage the legs were injured by exposure or in any other way, the lesions would ulcerate again. Each crop of lesions usually began simultaneously and healed simultaneously. The lesions were confined exclusively to the legs, and almost always to the lower third. There had been a few lesions over the dorsum of the foot and toes. The legs had never been completely healed during the winters of the past five years. However, they were completely healed in the summer of 1938, and remained so until late October. Although the healing was complete, a violaceous area would remain, and there the next year's crop of lesions would appear. These pigmented areas never disappeared. The severe pain would usually last until ulceration occurred and then progressively diminish.



Fig. 15.—Case 4. Photomicrograph ($\times 65$) of typical lesion. Note angiitis in subcutis, and fibrosis.

Physical examination showed nothing abnormal except the leg lesions. There were large, square-shaped, granulating lesions on the inner aspect of the ankles, extending backward to the calves. There was marked ulceration of the ankles, dorsums of the feet, and toes. The dorsalis pedis and posterior tibial vessels were normal. There were no color changes when the feet were either elevated or dependent. There were slight varicose veins on both legs. The oscillometric readings were normal.

A roentgenogram of the lungs revealed nothing abnormal. The basal metabolic rate was plus 2 per cent, and the blood Wassermann reaction was negative. The erythrocyte count was 4,660,000; the leucocyte count, 9,550; the platelet count, 200,000; the hemoglobin, 77 per cent; and the color index, 0.78. The differential leucocyte count showed polymorphonuclears, 71 per cent; small lymphocytes, 28 per cent; and large lymphocytes, 1 per cent. Chemical examination of the blood revealed that the urea nitrogen was 10 mg.; the nonprotein nitrogen, 26 mg.; the inorganic phosphate, as P, 3.3 mg.; and the calcium, 10.7 mg., per 100 ml. of serum. Ascorbic acid studies showed a fasting blood content of 1.09 mg. per 100 ml. of plasma; in the saturation test, 430 mg. were excreted in the first five hours,

and a total of 475 mg. in the twenty-four hours following injection of 1,000 mg. (The normal amount of ascorbic acid excretion in the urine following a 1,000 mg. test dose is 480 or more mg. in five hours, and 500 or more mg. in twenty-four hours.³⁴) The sedimentation rate, by the Westergren method, was 15 mm. in sixty minutes. Fractional gastric analysis revealed a normal acidity curve. All the cold sensitivity tests (exposure to chilling and application of ice directly to the skin) were negative.

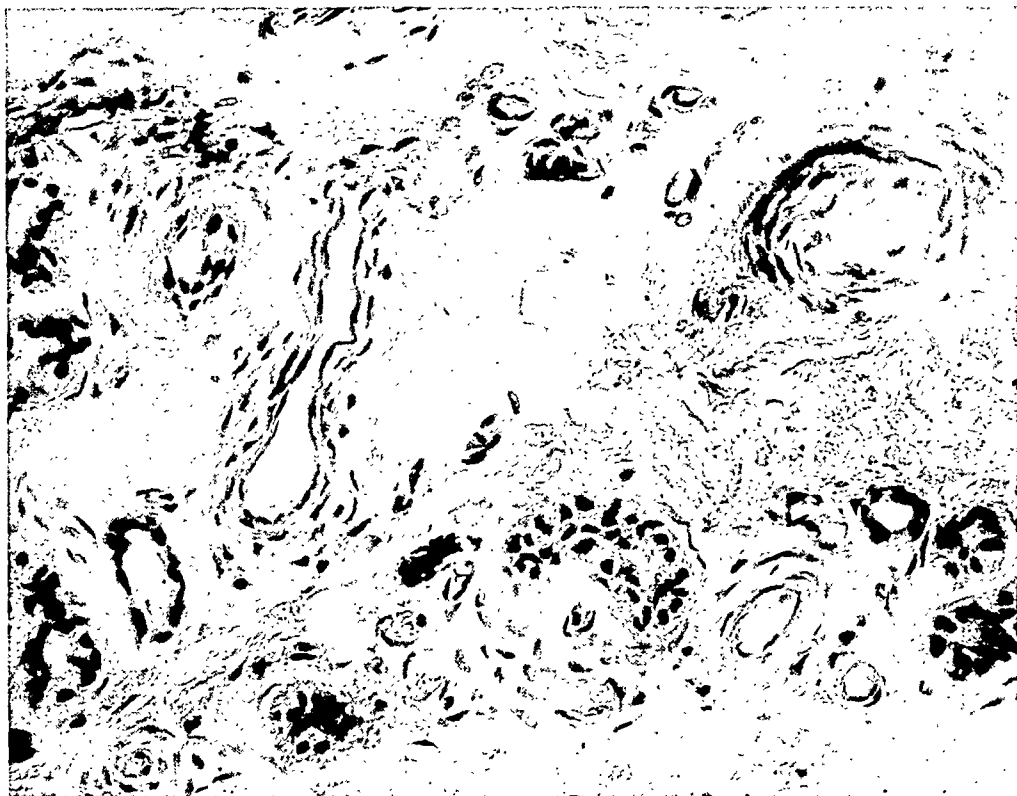


Fig. 16.—Case 4. Photomicrograph ($\times 650$), enlargement of box in Fig. 15. Isolated nests of epithelium. Endothelial proliferation and perivascular infiltration.

Biopsy of a lesion revealed no evidence of tuberculosis. There were superficial cornification and exfoliation of the stratified squamous epithelium. There was an increase of the fibrous tissue in the underlying corium, with marked edema and a smoothing of the rete pegs. The sweat glands were displaced and their coils were separated by the increased, edematous, connective tissue fibers. A mild degree of mononuclear cell infiltration was noted. The deeper layers of the epidermis were pigmented, and the lymph spaces between the cells were dilated, with a tendency to vesicle formation. The capillaries showed evidence of proliferation. In the subcutis the vessel walls were greatly thickened, which had caused occlusion of the lumina, and there was marked perivascular infiltration. The striking feature was an angitis.

DISCUSSION

These cases are strikingly similar in several respects. The leg lesions appeared in adolescence or early adulthood, and the attacks were precipitated by exposure to cold, usually coming in the late autumn. The condition continued throughout the winter, at which time the lesions were at the height of their activity.

The lesions lasted a varying length of time, but gradually subsided, until, in the late spring or early summer, they healed, leaving scar formation and pigmentation. In some cases the ulcers may have failed to heal completely during a summer. The next fall there was an exacerbation of symptoms and a recrudescence of lesions.

There were burning and itching, then redness, followed by the appearance of discrete, red, raised areas, with induration in which excruciating pain was felt. This was followed by a more pronounced elevation of the lesions, which became a deeper red or violaceous color while the skin became very thin. Next there was an exudate of pink or black-tinged serum, giving way to a yellowish exudate, true ulceration, and slow healing, with cessation of pain. Lastly, there were scar formation and deep pigmentation of the scarred area. Not infrequently these lesions failed to progress to actual ulceration.

In each case, the most prominent histologic feature of the biopsy specimen was an angiitis, with necrosis of the panniculus adiposus and a definite inflammatory reaction, but there was absolutely no evidence of a tuberculous condition.

Pernio has long been considered a dermatologic problem, when, in reality, it is a vascular problem, with secondary dermatologic manifestations. It has been rather inadequately described in the American literature, and seems to be of sufficient importance and interest to warrant a refocusing of attention on it.

The lesions have a disfiguring effect on the limbs, leaving them permanently scarred when the process is not in the stage of ulceration. This constitutes a mental handicap to its victims, in this day of thin stockings and short skirts. It is a debilitating condition, necessitating long periods in bed, or indoor rest, especially during the colder months of each year.

It is interesting that Corlett's patients had their lesions on the hands and wrists, while ours and most of the German patients recently reported had theirs on the legs. In 1896, during the cold weather, women wore long drawers, heavy stockings, high boots, long skirts, and coats; the only parts of the body exposed to the cold were the hands. Today, women do not usually wear long drawers, heavy stockings, or high-top shoes; skirts are never lower than calf length for everyday wear, and stockings are silk. The shoes are perforated and thin, with light soles. Consequently, from the mid-thigh down there is today little or no protection in a woman's clothing against the cold. This exposes a large area of the body surface to cooling, with a resultant great loss of heat by radiation. In order to help maintain a constant body temperature and prevent heat loss, the vessels in the legs are necessarily forced into vasoconstriction, resulting in anoxemia of the supplied tissues. This, in all probability, affects primarily the arterioles, and, secondarily, the tissues supplied by the minute vessels of the skin and the subcutaneous

zones, which bear the brunt of the anoxemia. The greater clothing protection which men customarily have probably accounts for the present rarity of pernio in the male sex.

SUMMARY

Evidence has been presented that pernio is a vascular disease, affecting the smaller vessels of the skin, causing anoxemia of the supplied tissue, and resulting in necrosis and ulceration. Later, a definite sclerodermic-like change in the skin may occur. It is precipitated by a downward change in temperature, not necessarily freezing, but by mere cooling. This may occur at a temperature which, under ordinary circumstances, would not cause an appreciable change in normal skin, but which causes definite changes in susceptible persons. Characteristically, exacerbations of this condition occur in the fall and winter, and regression in the summer. In long-standing cases, however, complete recovery may not occur in the summer. We believe that this is due to the extensive vascular changes in the tissues.

We have been able to demonstrate giant cells in our sections, but we have found no evidence of tuberculosis. We have very carefully checked our patients clinically with this in mind, so that we can make the definite statement that our patients were free from clinical and roentgenologic evidence of active tuberculosis at the time their leg lesions were active.

The following tentative criteria are suggested for the diagnosis of pernio.

1. It may occur in both sexes, predominantly in females.
2. It usually commences in adolescence or early adulthood.
3. It is associated with cool or cold weather and may show spontaneous recovery in warm weather.
4. The lesions have a predilection for exposed areas, particularly the lower third of the leg, around the internal malleolus and calf. They may extend down to the dorsum of the foot and toes, and up the legs to below the knees.
5. The clinical course of these lesions may be characterized briefly as (a) the formation of a reddened area which later becomes elevated, hard, and very painful; (b) this becomes violaceous and fluctuating; (c) it opens, producing an ulcer; (d) this oozes, drains, and heals, becoming less painful; (e) a violaceous scar remains; and (f) the following winter ulceration tends to recur in the same area.
6. There is a definite pathologic picture. Most characteristic is, first, an angiitis of the smaller vessels; secondly, necrosis of the fat; and, thirdly, the presence of giant cells. This pathologic picture, while characteristic of all our cases, must not be considered morphologically specific, for a number of other vascular conditions present similar histologic changes. They all represent a chronic irritative process in

the subepidermal tissue. Whether the irritative phenomenon is secondary or primary cannot be definitely stated.

Treatment of this condition is not specific, but the best results in our hands have been achieved by triweekly treatments with acetyl-beta-methylcholine chloride (mecholy) by iontophoresis, and by protection of the legs with proper clothing from undue exposure. Living in a warm climate should minimize the occurrence of the lesions.

Early recognition of this syndrome, and treatment as suggested, will help to prevent permanent disfigurement and long periods of incapacitation.

The authors are grateful to Dr. Harry M. Zimmerman, of Yale University Medical School, for his kindness in reviewing their pathologic material.

REFERENCES

1. Hallam, R.: Enigma of Chilblain, *Brit. M. J.* 1: 215, 1931.
2. (a) Hawthorn, M. M., and Vigne, P.: Un cas d'érythème induré de Bazin chez un jeune homme de 24 ans, *Marseille-méd.* 1: 696, 1934.
(b) Vigne, P., and Dusan, J.: Un autre cas d'érythème induré de Bazin type Hutchinson, *Marseille-méd.* 1: 699, 1934.
3. Bazin, A. P. E.: *Lecons theorique et cliniques sur le scrofule*, ed 2, Paris, 1861, A. Delahaye.
4. Pautrier, L. M., and Yelmo, A.: Bazin's Erythema of Both Legs in Patients Who Previously Had Symmetrical Supramalleolar Erythrocyanoses, *Bull. Soc. franç. de dermat. et syph.* 42: 859, 1935.
5. Telford, E. D.: Erythrocyanosis, *Brit. Encyc. Med. Practice* 5: 182, 1937.
6. David, Jean: Erythrocyanose sur malleolaire étude pathogenique, clinique et Therapeutique, 24 cm., No. 63, Paris, 1929, Jouve & Cie.
7. Schulde, Reinhold: Ueber Erythrocyanosis Cutis Symmetrica mit besonderer Berücksichtigung zweier Falle, *Frankfurt Theses*, Frankfurt a. M., Werner u. Winter, 1927.
8. Corlett, W. T.: Cold as an Etiological Factor in Diseases of the Skin, *Tr. Am. Dermat. A.* 18: 95, 1894.
9. Gallois, P.: Engelure des jambres, *J. méd. de Paris* 48: 532, 1929.
10. Grschebin, S.: Concerning the Identity of Erythema Induratum of Bazin and Lupus Pernio, *Urol. & Cutan. Rev.* 39: 477, 1935.
11. Bartman, Joseph: Contribution à l'étude du lupus pernio, *Paris Theses*, Paris, 1925, Ed. Medicales.
12. Bescone, Jeanne: Contribution à l'étude du lymphogranulome Benin (lupus pernio vrai), *Paris Theses*, Paris M. Lac, 1928.
13. Nardelli, L.: Bazin's erythema induratum and acrocyanosis, *Gior. ital. di dermat. e sif.* 67: 83, 1926.
14. Klingmuller, F., and Dittrich, O.: Ueber Frostschaeden, *Dermat. Ztschr.* 49: 1, 1926.
15. Perutz, A.: Ueber eine eigenartige Lokalisation von Frostschaeden, *Dermat. Wehnschr.* 88: 709, 1929.
16. Kreindler, A., and Elias, H.: Zur Klinik und Pathogenese der juvenilen Acrocyanose, *Ztschr. f. Kinderh.* 50: 608, 1931.
17. Ravitch, M. L.: Focal Infection in Relation to Certain Dermatoses, *J. A. M. A.* 67: 430, 1916.
18. Haldin, Davis: Skin Diseases in the Winter, *Practitioner* 141: 741, 1938.
19. Woringen, F.: Histological Picture of Bazin, *Bull. Soc. franç. de dermat. et Syph.* 45: 1316, 1938.
20. Corlett, W. T.: Cold as an Etiological Factor in Diseases of the Skin, 1894, Eleventh International Medical Congress in Rome, p. 153.
21. Corlett, W. T.: Dermatitis Hiemalis With a Consideration of Its Pathological Anatomy, 1896, Third International Congress of Dermatology in London, p. 622.
22. Niles, H. D.: Winter Eczema of the Arms, *Arch. Dermat. & Syph.* 39: 474, 1939.

23. (a) Telford, E. D., and Stopford, J. S. B.: Some Experiences of Sympathectomy in Anterior Poliomyelitis, *Brit. J. Surg.* 18: 557, 1931.
- (b) Telford, E. D., and Stopford, J. S. B.: Some Experiences of Sympathectomy in Anterior Poliomyelitis, *Brit. M. J.* 2: 770, 1933.
- (c) Telford, E. D.: Lesions of the Skin and Subcutaneous Tissue in Diseases of the Peripheral Circulation, *Arch. Dermat. & Syph.* 36: 952, 1937.
24. Eugman, M. F.: The Skin: A Mirror to the System, *J. A. M. A.* 73: 1565, 1919.
25. Von Norden, W.: Die neuere frostbeulen Behandlung, *München. med. Wehnschr.* 75: 691, 1928.
26. Dittrich, O.: Ueber Frostschaeden, *Arch. f. Dermat. u. Syph.* 157: 1, 1929.
27. Lewis, Thomas: Observations Upon the Reactions of the Vessels of the Human Skin to Cold, *Heart* 15: 177, 1929.
28. Fischl, F.: Identity of Dermatitis Nodularis Necrotica and Papulonecrotic Tuberculid, *Dermat. Wehnschr.* 92: 50, 1931.
29. Mayer, R. L., and Cajkovac, S.: Seasonal Variation in Nonspecific Sensibility of the Skin in Eczema and Related Diseases, *Arch. f. Dermat. u. Syph.* 126: 325, 1932.
30. Cajkovac, S., and Mayer, R. L.: Seasonal Differences in Skin Sensibility and in Frequency of Eczematous Diseases, *Liječn vjes* 54: 268, 1932.
31. Sannicandro, G.: Hitherto Undescribed Skin Diseases, Pigmented Papuloverrucous Dermatoses With Connective Tissue Hyalinosis, *Arch. f. Dermat. u. Syph.* 166: 58, 1932.
32. Buerger, Leo: Chilblain, *Nelson Loose-Leaf Medicine* 2: 664C-K, 778A-I, 1937.
33. Knight, G. C.: Sympathectomy in the Treatment of Erythrocyanosis Frigida and Chronic Oedema of the Leg, *St. Barth. Hosp. Rep.* 71: 173, 1938.
34. Wright, I. S., Lilienfeld, A., and MacLenathen, E.: Determination of Vitamin C Saturation: A Five Hour Test After an Intravenous Test Dose, *Arch. Int. Med.* 60: 264, 1937.

DISCUSSION

DR. IRVING S. WRIGHT, New York.—The last two papers emphasize the fact that livedo reticularis and pernio in particular, and I believe this holds for numerous other conditions, have been in the past erroneously considered as diseases of the skin, and treated primarily by the dermatologist, frequently by means of the application of salves, ointments, and perhaps superficial roentgen therapy.

Now, this is not to be regarded primarily an endeavor on the part of the workers in the field of vascular disease to try to move these diseases from one specialty to another, but it is important that we change our conception of them. In other words, as long as we treat these diseases as if they were only superficial local lesions, and do not understand the fundamental vascular changes underlying them, I can see no hope for solution either from the viewpoint of the pathology, etiology, or treatment.

That, in itself, constitutes in my mind a very important contribution to thought in this field, and I do not doubt that other so-called skin diseases will yield to similar types of study. Certainly that has been true of lupus erythematosus disseminatus, which has been studied so capably by Libman and Sachs and others.

DR. NORMAN E. FREEMAN, Philadelphia.—Since Dr. McGovern and Dr. Wright feel that this condition is associated with normal vasoconstricting activity, I wonder if they have had any experience with sympathectomy in the treatment.

We recently saw a patient who had a combination of livedo reticularis and pernio, on whom we did a paravertebral novocaine block, anesthetizing the sympathetic lumbar ganglia. With the blanching of the reticular areas of the livedo reticularis, there was also a change from the cyanotic appearance of these lesions of pernio to a nice, pink color.

DR. NELSON W. BARKER, Rochester, Minn.—Although the clinical pictures of pernio and livedo reticularis are different, I am much impressed with the similarity of the pathologic changes in the arterioles of the skin. There is reason for believing that

this type of vascular lesion is not a specific one, for it is also seen in a number of other conditions in which the clinical pictures are different from one another. In livedo reticularis, the temperature of the skin is subnormal for long periods of time, both when the patient is exposed to cold and when he is in a normal environmental temperature. It is possible that this lowered temperature of the skin may be a factor in the production of the pathologic changes in the arterioles.

DR. HAROLD D. LEVINE, Concord, N. H.—I should like to ask Dr. McGovern whether these patients were tested for sensitivity to cold ("cold allergy"), and whether she has any information as to the nature of the condition in its very inception. It would be of interest to know if in the early attacks the lesions are urticarial.

DR. TERESA MCGOVERN, New York.—Sympathectomy was not performed in any of our cases of pernio; consequently, we are not in a position to pass comment on this type of therapy. The lesions in pernio are not of an urticarial character, but are merely erythematous. This lesion has none of the characteristics of true cold allergy, as first described by Horton and Brown. The cold tests were done on all of these patients and none was sensitive to cold, as we understand cold sensitivity.

INCIDENCE OF TYPES OF HEART DISEASE AMONG 30,265
AUTOPSIES, WITH SPECIAL REFERENCE
TO AGE AND SEX

B. J. CLAWSON, M.D.
MINNEAPOLIS, MINN.

THE relative frequency of the various types of heart disease evidently is not the same in all localities. Rheumatic types are more common in the northeastern states than in Minnesota, and syphilitic types are more common in some of the southern states.

It is difficult to obtain reliable information concerning the incidence of heart disease from death certificates because of the uncertainties of diagnosis. It is also difficult to find a large, nonselected, autopsy series.

White,¹ in analyzing the literature on the incidence of the types of heart disease, stated: "Accurate information about the community incidence of heart disease is as yet scarcely available anywhere in the world."

The purpose of the analysis in this paper is to give the incidence of the types of cardiac disease encountered among the autopsies which have been performed at the University of Minnesota Medical School during 1910 to 1938, inclusive. During this period there were 19,685 autopsies on males and 10,580 on females, or a total of 30,265, not including those on stillborn infants. In this same period there were 4,678 deaths from nonecongenital cardiac disease (15.45 per cent of the autopsies). Congenital heart disease is not included because it occurred mainly in stillborn babies; the small number of cases in persons older than babies would increase the general incidence by less than 0.5 per cent.

The only cases included were those in which death was caused by cardiac failure, or by conditions fairly definitely associated with cardiac failure, such as uremia, or cerebral hemorrhage with hypertension, or rupture of a syphilitic aneurysm of the arch of the aorta. In most of these, when death was not due entirely to conditions in the heart itself, there was an overlapping of heart disease, so that death would evidently have resulted soon from cardiac failure. Cases of valvular deformities or cardiac hypertrophy in which death was caused by something other than heart disease, such as an automobile accident, were not included. The actual incidence of cardiac disease in this series was, therefore, even greater than that reported in this paper.

From the Department of Pathology, University of Minnesota.
Received for publication Feb. 3, 1941.

The percentage of cardiac deaths in this autopsy series, we believe, is near to the percentage of cardiac deaths in the general population in the State of Minnesota. The autopsy material was fairly representative and nonselected. The autopsies were done in general and private hospitals, on private patients of practicing physicians, and on the coroner's service, which was fairly large. In 1938 the percentage of autopsies was high, namely, 25 per cent in Minneapolis and 10 per cent in the State of Minnesota. The percentages in the preceding years, while somewhat less, were also high. This material, because of its volume, wide distribution, and large autopsy percentage, appears to be as good as any that could be found for making an approach to a statistical study of the incidence of the different types of cardiac disease.

All cardiac autopsy records were restudied. Many of the cases were observed personally.

The 4,678 cases were analyzed with respect to causes and incidence of types and to age and sex incidence. They were divided into two main groups, namely, the infectious, consisting of 1,726 cases (36.9 per cent), and the noninfectious (Table I), consisting of 2,952 cases (63.1 per cent). Relatively, the cases of noninfectious heart disease increased from 55 per cent to 63.1 per cent from the time the total number of cardiac deaths was 3,380, about ten years ago, to the end of 1938, when the number was 4,678 cases.

I. INFECTIOUS HEART DISEASE

The infectious group comprises those classed as (A) rheumatic, (B) bacterial, (C) syphilitic, and (D) "toxic myocardium" (Table I).

A. *Rheumatic Heart Disease* includes the kind of valvulitis immediately associated with acute rheumatic fever or chorea, the different kinds of valve deformities, and the cases in which death resulted entirely or primarily from an adherent pericardium.

In acute and recurrent rheumatic endocarditis there is acute infection, with active valvulitis and vegetations. In the recurrent type there are acute verrucous vegetations on valves which grossly show previous thickening. The various kinds of valve deformities are caused by repeated attacks of rheumatic proliferative inflammation.

There were 870 cases of rheumatic heart disease in the entire group. This was 50.4 per cent of the infectious group and 18.6 per cent of the entire 4,678 cases. The rheumatic group (Table I) was divided into (1) acute rheumatic endocarditis, ninety-eight cases (11.3 per cent of rheumatic group and 2.1 per cent of total), (2) recurrent rheumatic endocarditis, eighty-five cases (9.8 per cent of rheumatic and 1.8 per cent of total), (3) valve deformities, 650 cases (74.7 per cent of rheumatic and 13.9 per cent of total), and (4) adherent pericardium, thirty-seven cases (4.2 per cent of rheumatic and 0.8 per cent of total). There

TABLE I
CARDIAC DISEASES (4,678 CASES)

TYPES	PERCENTAGE OF GROUPS			PERCENTAGE OF TOTAL GROUP		
I. Infectious (1,726)				36.9		
A. Rheumatic (870)	50.4			18.6		
1. Acute rheumatic (98)		11.3			2.1	
2. Recurrent rheumatic (85)		9.8			1.8	
3. Valve deformities (650)		74.7			13.9	
a. Incompletely healed Class I (125)			19.2			2.7
b. Completely healed Class II (265)			40.8			5.7
c. Calcific nodular aortic Class III (260)			40.0			5.5
4. Adherent pericardium (37)		4.2			0.8	
B. Bacterial (514)	29.8			11.0		
1. Primary acute (49)		9.5			1.0	
2. Secondary acute (101)		19.6			2.2	
3. Subacute (364)		70.8			7.8	
C. Syphilitic (327)	18.9			7.0		
1. Aortic insufficiency (180)		55.0			3.8	
2. Narrowing of coronary orifices (74)		22.6			1.6	
3. Rupture of aortic aneurysm (68)		20.8			1.5	
4. Gumma of myocardium (5)		1.5			0.1	
D. Toxic myocardium (15)	0.9			0.3		
II. Noninfectious (2,952)				63.1		
A. Hypertensive, primary (2,597)	88.0			55.5		
1. Myocardial insufficiency (1,124)		43.3			24.0	
a. B.P. 150 or more (747)			66.6			16.0
b. B.P. below 150; heart weight, M 500 or more; F 450 or more (149)			13.3			3.0
c. B.P. unknown; heart weight as in (b) (163)			14.5			3.6
d. B.P. unknown; heart weight M below 500; F, below 450 (65)			5.8			1.3
2. Coronary sclerosis (935)		36.0			20.0	
a. B.P. 150 or more (285)			30.5			6.1
b. B.P. below 150 or unknown; heart weight M 500 or more; F 450 or more (290)			31.0			6.2
c. B.P. as in b; heart weight M 400-499; F 350-449 (360)			38.5			7.6
3. Encephalopathy (apoplexy) (362)		13.9			7.7	
a. B.P. 150 or more (296)			81.8			6.3
b. B.P. low or unknown; heart weight M 500 or more; F 450 or more (66)			18.2			1.4
4. Renal insufficiency (176)		6.8			3.8	
B. Coronary sclerosis; B.P. below 150; heart weight M below 400; F below 350 (280)	9.5			6.2		
C. Pulmonary hypertension (69)	2.3			1.5		
D. Miscellaneous (6)	0.2					
1. Thyroid heart (6)		100.0				
a. Hyperthyroid (5)			83.4			
b. Hypothyroid (1)			16.6			
2. Primary renal disease						
a. Glomerulonephritis (0)						
3. Beriberi heart (0)		0.0	0.0			
4. Cardiac hypertrophy and dilatation without hypertension		?				

were three classes of valve deformities (Table I), namely (a) the incompletely healed valve deformities, 125 cases (19.2 per cent of valve deformities and 2.7 per cent of total), (b) the completely healed valve deformities, 265 cases (40.8 per cent of valve deformities and 5.7 per cent of total), and (c) the calcific, nodular, aortic valve deformity, 260 cases (40 per cent of valve deformities and 5.5 per cent of total). Classes *a* and *b* might as well be considered together, for microscopic examination shows that some degree of activity is common to most of the valve deformities. Class *c* is regarded by some observers as not of rheumatic origin. We have analyzed this group previously, and have failed to find any reason why it should not be classed as rheumatic. Structurally, the calcific, nodular, aortic valve deformity cannot be differentiated from calcific mitral lesions. If the calcific aortic valve deformity is not of rheumatic origin, one would have to conclude that the aortic valve is seldom infected with the rheumatic infectious agent. The calcific, nodular type of lesion is the one usually seen as a non-syphilitic aortic valve deformity.

Age and Sex (Table II). Acute rheumatic endocarditis is primarily a disease of young persons. Thirty-two of the forty-eight males (66.7 per cent) and thirty-one of the fifty females (62 per cent) died in the first two decades. Seven males and fourteen females died in the third and fourth decades. Only nine of the forty-eight males and five of the fifty females died in decades above the fourth. In a large series of autopsies over a period of several years, acute rheumatic endocarditis is seldom found in older persons, but in our series of ninety-eight cases one man and two women died in the ninth and tenth decades.

The number of each sex who died of the various types of heart disease was compared with the total number of respective male or female autopsies from which the cardiac cases were taken during the same period. This method gave a more nearly correct percentage, or rate per thousand, of autopsies, and probably of the general population, than the percentage of the total number of cases which occurred in each sex in each type, for, in the upper decades, more autopsies were performed on men than on women. There were 19,685 autopsies on males and 10,580 on females. In comparing the proportion of the sex incidence, the number per thousand (M) rather than the percentage (%) was used for the purpose of making the difference more apparent.

In the acute rheumatic group there were 2.4 males per thousand and 4.7 females per thousand, or about two females to one male. This is a significant difference. In only one of the decades, the third, was the difference significant, i.e., 2.3 males per thousand and 8.5 females per thousand.

In cases of recurrent rheumatic endocarditis death occurred somewhat later than from acute rheumatic endocarditis. The greatest number of males per decade was in the second and fourth, and, of females,

TABLE II
AGE AND SEX INCIDENCE IN TYPES OF RHEUMATIC HEART DISEASE (870 CASES)

DECADE	AUTOPSIES	A.R.		R.R.		VD "a"		VD "b"		VD "c"		AD. PER.		TOTAL	
		NO.	M	NO.	M	NO.	M	NO.	M	NO.	M	NO.	M	NO.	M
Males (522 Cases)															
1	2,978	15	5.0	0	0.0	1	0.3	0	0.0	0	0.0	3	1.0	19	6.4*
2	645	17	26.3	9	13.9	1	1.5	2	3.1	2	3.1	6	9.3	37	57.3
3	1,324	3	2.3*	8	6.0	8	6.0	16	12.1	8	6.0	6	4.5*	49	37.0
4	2,052	4	1.9	9	4.4	11	5.4*	27	13.1	26	12.7*	3	1.5	80	39.0
5	3,132	1	0.3	6	1.9*	23	7.3	40	12.8*	40	12.8*	5	1.6	115	36.7*
6	3,439	3	0.9	6	1.7	14	4.1	22	6.4*	47	13.7*	3	0.9	95	27.6*
7	3,350	3	0.9	2	0.6	4	1.2*	8	2.4*	45	13.4*	0	0.0	62	18.5
8	2,172	1	0.5	1	0.5	5	2.3	6	2.8	42	19.3*	2	0.9	57	26.2
9	565	1	1.8	0	0.0	1	1.8	2	3.5	4	7.1	0	0.0	8	14.2
10	28	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Total	19,685	48	2.4*	41	2.1*	68	3.4*	123	6.2*	214	10.9*	28	1.4	522	26.5*
Females (348 Cases)															
1	2,208	16	7.2	4	1.8	1	0.4	2	0.9	0	0.0	0	0.0	23	10.4*
2	574	15	26.1	13	22.6	1	1.7	4	7.0	1	1.7	3	5.2	37	64.5
3	1,174	10	8.5*	6	5.1	5	4.2	19	16.2	4	3.4	1	0.8*	45	38.3
4	1,283	4	3.1	5	3.9	14	10.9*	23	18.0	3	2.3*	0	0.0	49	38.2
5	1,347	1	0.7	10	7.4*	14	10.4	39	28.9*	5	3.7*	2	1.5	71	52.7*
6	1,411	0	0.0	4	2.8	11	7.8	30	21.3*	11	7.8*	2	1.4	58	41.1*
7	1,342	1	0.7	1	0.7	7	5.2*	17	12.7*	9	6.7*	0	0.0	35	26.1
8	930	0	0.0	1	1.1	4	4.3	6	6.4	7	7.5*	1	1.1	19	20.4
9	279	2	7.2	0	0.0	0	0.0	2	7.2	5	18.0	0	0.0	9	32.2
10	32	1	31.2	0	0.0	0	0.0	0	0.0	1	31.2	0	0.0	2	62.5
Total	10,580	50	4.7*	44	4.1*	57	5.4*	142	13.4*	46	4.3*	9	0.8	348	32.9*

*A significant difference.

in the second, but it is to be noted that the number was relatively large from the second to the sixth for the males (thirty-eight, or 92.7 per cent) and from the second to the fifth for the females (thirty-four, or 77.3 per cent).

In the recurrent rheumatic cases, as in the acute rheumatic group, the females outnumbered the males. There were 2.1 males per thousand autopsies on males, and 4.1 females per thousand autopsies on females. The only decade in which there was a significant sex difference was the fifth, in which there were 1.9 males per thousand and 7.4 females per thousand.

In the group of incompletely healed valve deformities (*a*) the greatest number of males per decade was in the fifth and of females in the fourth and fifth. Forty-eight of the sixty-eight males (70.6 per cent) and thirty-nine of the fifty-seven females (68.4 per cent) died in the fourth, fifth, and sixth decades.

In this group, also, there were more females than males (3.4 males per thousand and 5.4 females per thousand, which is a significant difference). A significant sex difference was noted in the fourth decade (5.4 males per thousand and 10.9 females per thousand). In the second division of valve deformities (*b*), those with completely healed valves, the greatest number per decade in both sexes died in the fifth, which is about the same as in division *a*. One hundred thirteen of the 123 males (91.8 per cent) and 128 of the 142 females (90.1 per cent) in the valve deformities group (*b*) died in the third, fourth, fifth, sixth, and seventh decades.

In this second class (*b*) of valve deformities there were 6.2 males per thousand autopsies on males, and 13.4 females per thousand autopsies on females, which is a significant difference. There was also a significant sex difference in three of the decades, namely, the fifth (12.8 males and 28.9 females per thousand), the sixth (6.4 males and 21.3 females per thousand), and the seventh (2.4 males and 12.7 females per thousand).

In the calcific, nodular, aortic valve deformity class (*c*), the greatest number of deaths per decade in both sexes occurred in the sixth. Two hundred of the 214 males (93.7 per cent) died in the fourth, fifth, sixth, seventh, and eighth decades, and thirty-seven of the forty-six females (80.4 per cent) in the fifth, sixth, seventh, eighth, and ninth decades. It is evident that persons in this group live longer than those in the two preceding classes.

Contrary to what was found in classes *a* and *b*, in class *c* the males greatly outnumbered the females. There were 10.9 males per thousand autopsies on males, and 4.3 females per thousand autopsies on females, which is a definite, significant difference. There was also a significant sex difference in five of the decades, namely, the fourth (12.7 males and 2.3 females per thousand), the fifth (12.8 males and 3.7 females per thousand), the sixth (13.7 males and 7.8 females per thousand),

the seventh (13.4 males and 6.7 females per thousand), and the eighth (19.3 males and 7.5 females per thousand).

In the thirty-seven cases in which death was caused by an adherent pericardium, the greatest number of males per decade died in the second and third decades. The highest per decade for the females was in the second. In this group there were 1.4 males per thousand autopsies on males, and 0.8 females per thousand autopsies on females. This difference was not significant. There was probably a significant sex difference in the third decade (4.5 males and 0.8 females per thousand).

In the entire rheumatic group of 870 cases, the greatest number per decade in both sexes was in the fifth.

There was probably a significant sex difference (26.5 males and 32.9 females per thousand autopsies), but this difference of 6.4 per thousand was relatively small. A probably significant sex difference in the total rheumatic group was noted in three decades, namely, the first (6.3 males and 10.4 females per thousand), the fifth (36.7 males and 52.7 females per thousand), and sixth (27.6 males and 41.1 females per thousand).

B. Bacterial Endocarditis may be similar etiologically to acute or recurrent rheumatic endocarditis, but since the bacterial type runs a different clinical course and shows different clinical manifestations, the diseases should be considered as separate entities. Patients with bacterial endocarditis develop a secondary anemia, have embolic processes in the spleen, kidneys, brain, lungs, and intestines, run a septic course, and die, as a rule, within less than two years. The microscopic structural inflammatory reaction within the valves is similar to that in the valves in acute rheumatic endocarditis, but the vegetations are larger and soft, and, as a rule, contain many colonies of bacteria. This large, heavily infected vegetation, we believe, accounts for the clinical and anatomic differences between acute rheumatic endocarditis and bacterial endocarditis.

There were 514 cases of bacterial endocarditis (29.8 per cent of the infectious cases and 11 per cent of the total). On clinical grounds, the cases of bacterial endocarditis were divided into three classes, namely, (1) primary acute bacterial endocarditis, in which death occurred within less than six weeks after the beginning of symptoms, forty-nine cases (9.5 per cent of the bacterial and 1.0 per cent of the total), (2) secondary acute bacterial endocarditis, in which there was some other infection or some wasting disease, 101 cases (19.6 per cent of the bacterial and 2.2 per cent of the total), and (3) subacute bacterial endocarditis, in which the symptoms had lasted more than six weeks, 364 cases (70.8 per cent of the bacterial and 7.8 per cent of the total). The two acute classes differ to some extent from the subacute class. The organism usually found in the blood of patients with subacute bacterial endocarditis is the *Streptococcus viridans*. *Streptococcus hemolyti-*

cus, *Staphylococcus aureus*, and the gonococcus are more commonly found in the clinically acute types.

Age and Sex (Table III).—The greatest number of males per decade in the group of cases of primary acute bacterial endocarditis died in the fifth decade, and the greatest number of females in the fourth. In both sexes the majority of deaths occurred in the earlier decades.

TABLE III

AGE AND SEX INCIDENCE IN TYPES OF BACTERIAL ENDOCARDITIS (514 CASES)

DECADE	AUTOPSIES	PRIMARY ACUTE		SECONDARY ACUTE		SUBACUTE		TOTAL	
		NO.	M	NO.	M	NO.	M	NO.	M
Males (312 Cases)									
1	2,978	1	0.3	1	0.3	3	1.0	5	1.7
2	645	3	4.6	1	1.5	13	20.1*	17	26.3*
3	1,324	3	2.3	6	4.5*	45	34.0	54	40.8
4	2,052	3	1.5*	11	5.4*	53	25.6	67	32.6
5	3,132	8	2.5	8	2.5	53	17.0	69	22.0
6	3,439	2	0.6	10	2.9	39	11.3*	51	14.8
7	3,350	4	1.2	8	2.4	27	8.1*	39	11.6
8	2,172	1	0.5	3	1.4	2	0.9	6	2.8
9	565	0	0.0	2	3.5	2	3.5	4	7.1
10	28	0	0.0	0	0.0	0	0.0	0	0.0
Total	19,685	25	1.3*	50	2.5*	237	12.0	312	15.8*
Females (202 Cases)									
1	2,208	2	0.9	2	0.9	3	1.3	7	3.2
2	574	4	7.0	2	3.5	22	38.3*	28	48.8*
3	1,174	5	4.2	16	13.6*	38	32.4	59	50.2
4	1,283	8	6.2*	14	10.9*	28	21.8	50	40.0
5	1,347	0	0.0	5	3.7	18	13.4	23	17.1
6	1,411	1	0.7	7	5.0	9	6.4*	17	12.0
7	1,342	2	1.5	4	3.0	6	4.5*	12	8.9
8	930	2	2.1	0	0.0	2	2.1	4	4.3
9	279	0	0.0	1	3.6	1	3.6	2	7.2
10	32	0	0.0	0	0.0	0	0.0	0	0.0
Total	10,580	24	2.3*	51	4.8*	127	12.0	202	19.1*

*A significant difference.

In this group the females predominated (1.3 males and 2.3 females per thousand autopsies). The outstanding and significant sex difference was in the fourth decade (1.5 males and 6.2 females per thousand autopsies).

In the group of cases of secondary bacterial endocarditis the majority of deaths in both sexes occurred in the earlier decades. The greatest number of males per decade was in the fourth, and, of the females, in the third.

As in the preceding group, the females outnumbered the males (2.5 males and 4.8 females per thousand autopsies). The greatest difference was in the third decade (males 4.5 and females 13.6 per thousand autopsies). The next greatest sex difference was found in the fourth decade (5.4 males and 10.9 females per thousand autopsies). In the total and in both of these decades the sex differences were significant.

In the 364 cases of subacute bacterial endocarditis, the greatest number of males per decade died in the fourth and fifth, and the greatest number of females in the third. Death occurred earlier in the females.

The sex incidence in the entire group was the same (twelve per thousand autopsies in both). There was a probably significant sex difference in three decades, namely, the second (20.1 males and 38.3 females per thousand autopsies), the sixth (11.3 males and 6.3 females per thousand autopsies), and the seventh (8.1 males and 4.5 females per thousand autopsies). It is to be noted that in the earlier decade, the second, the females predominated, and, in the later, the sixth and seventh, the males predominated.

In the entire group of 514 cases of bacterial endocarditis, acute and subacute, there was a significant sex difference (15.8 males and 19.1 females per thousand autopsies). A significant sex difference was noted in only one decade, the second (26.3 males and 48.7 females per thousand autopsies). The sex difference in the total number was due to the incorporation of the cases of primary and secondary acute endocarditis.

C. Syphilitic Heart Disease (Table IV).—The third group of cases of infectious heart disease are those of cardiac failure in which, except in one case, a gumma of the myocardium, syphilitic aortitis was present. There were 327 of these cases (18.9 per cent of the infectious heart disease and 7 per cent of the total).

Depending upon the manner in which death occurred, these syphilitic heart diseases fell into four groups: (1) aortic insufficiency caused by syphilitic valvulitis, 180 cases (55 per cent of the syphilitic cases and 3.8 per cent of the total); (2) narrowing of the coronary orifices, seventy-four cases (22.6 per cent of the syphilitic cases and 1.6 per cent of the total); (3) rupture of a syphilitic aneurysm, sixty-eight cases (20.8 per cent of the syphilitic cases and 1.5 per cent of the total); and (4) gumma of the myocardium, five cases (1.5 per cent of the syphilitic cases and 0.1 per cent of the total). There was a good deal of overlapping in the first three classes.

Age and Sex.—The greatest number of males with aortic insufficiency died in the sixth decade. The greatest number of the females died in the sixth and seventh decades. The majority of the males died in the fourth, fifth, sixth, and seventh decades, and the majority of females in the fifth, sixth, and seventh.

The males in this division greatly outnumbered the females (8.0 males and 2.2 females per thousand autopsies). The two decades in which there was a significant sex difference were the fifth (14.4 males and 4.5 females per thousand) and the sixth (18.3 males and 5.0 females per thousand).

In the group in which death was caused primarily by narrowing of the coronary orifices, the greatest number per decade in both sexes

occurred in the fourth. The majority in both sexes died in the fourth, fifth, sixth, and seventh decades.

There was a preponderance of males, but it was not so great as in the aortic insufficiency group (2.8 males and 1.7 females per thousand). A significant sex difference was noted in the fourth decade (6.3 males and 2.3 females per thousand).

TABLE IV

AGE AND SEX INCIDENCE IN TYPES OF SYPHILITIC HEART DISEASE (327 CASES)

DECADE	AUTOP- SIES	SYPHILIS (A)		SYPHILIS (B)		SYPHILIS (C)		SYPHILIS (D)		TOTAL	
		NO.	M	NO.	M	NO.	M	NO.	M	NO.	M
Males (274 Cases)											
1	2,978	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2	645	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
3	1,324	2	1.5	1	0.7	0	0.0	1	0.7	4	3.0
4	2,052	16	7.8	13	6.3*	4	1.9	1	0.5	34	16.6*
5	3,132	45	14.4*	25	8.0	21	6.7*	0	0.0	91	29.1*
6	3,439	63	18.3*	12	3.5	13	3.8	0	0.0	88	25.6*
7	3,350	29	8.6	5	1.5	17	5.1*	0	0.0	51	15.2*
8	2,172	1	0.5	0	0.0	4	1.8	0	0.0	5	2.3
9	565	1	1.8	0	0.0	0	0.0	0	0.0	1	1.8
10	28	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Total	19,685	157	8.0*	56	2.9*	59	3.0*	2	0.1	274	13.9*
Females (53 Cases)											
1	2,208	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2	574	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
3	1,174	2	1.7	1	0.8	0	0.0	0	0.0	3	2.6
4	1,283	1	0.8	3	2.3*	0	0.0	2	1.5	6	4.7*
5	1,347	6	4.4*	7	5.2	2	1.5*	1	0.7	16	11.9*
6	1,411	7	5.0*	3	2.1	4	2.8	0	0.0	14	9.9*
7	1,342	7	5.2	3	2.2	3	2.2*	0	0.0	13	9.7*
8	930	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
9	279	0	0.0	1	3.6	0	0.0	0	0.0	1	3.6
10	32	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Total	10,580	23	2.2*	18	1.7*	9	0.8*	3	0.3	53	5.0*

*A significant difference.

In the cases in which death occurred mainly from rupture of a syphilitic aortic aneurysm, the greatest number of males per thousand was in the fifth decade, and females in the sixth. Most of the deaths in both sexes occurred in the fifth, sixth, and seventh decades.

The males predominated (3 males and 0.8 females per thousand). There were two decades in which a significant sex difference was noted, namely, the fifth (6.7 males and 1.5 females per thousand) and the seventh (5.1 males and 2.2 females per thousand).

There were only five cases of syphilitic cardiac disease in which death was caused by gumma of the myocardium (two males and three females). The males died in the third and fourth decades, and the females in the fourth and fifth.

D. Toxic Myocardium.—Death from toxic myocardium, the fourth group of cases of infectious cardiac disease, was rare. This group was

included with the cases of infectious disease because the lesion, in this series, generally resulted from the effect of diphtheria toxin upon the heart muscle. There were fifteen cases (0.9 per cent of the infectious cases and 0.3 per cent of the total).

II. NONINFECTIOUS HEART DISEASES

The noninfectious cardiac diseases (Table II) caused most of the cardiac failure in this series. The percentage of this group has increased from 55 per cent to 63 per cent in the autopsy material in the last ten years. There were 2,952 cases (63.1 per cent of the total cardiac deaths) in the noninfectious heart disease group.

This group of 2,952 cases was composed of (*A*) hypertensive heart disease, (*B*) coronary sclerosis without hypertension, (*C*) pulmonary hypertensive heart disease, and (*D*) miscellaneous forms, such as heart disease associated with (*a*) hyperthyroidism or (*b*) hypothyroidism (Table I).

A. Hypertensive Heart Disease.—This large group includes the cases in which death was brought about by the effects of high blood pressure, primarily on the heart muscle. Cardiac hypertrophy and dilatation were usually present in these cases, but many of the patients died from coronary sclerosis, cerebral hemorrhage, or uremia. These cases have been classed as cardiac hypertrophy and dilatation, and chronic myocarditis, but, since in the majority there was an intimately associated hypertension, it seems preferable to classify them as cases of hypertensive heart disease. There were 2,597 cases (88 per cent of the noninfectious cases and 55.5 per cent of the total).

Depending upon the manner in which death occurred, the group has been divided into four divisions: (1) myocardial insufficiency, (2) coronary sclerosis with hypertension, (3) encephalopathy (apoplexy), and (4) renal insufficiency.

1. *Myocardial Insufficiency.*—In these cases, with few exceptions, there were hypertrophy and dilatation of the heart and congestive failure. There were 1,124 cases (43 per cent of the hypertensive group and 24 per cent of the total). The 1,124 cases were classed as hypertensive heart disease on the basis of a history of elevation of the blood pressure and upon the weight of the heart. A few cases in which there were congestive heart failure, but small hearts and no record of increased blood pressure, were also grouped with the hypertensive cases. A systolic blood pressure of 150 mm. Hg, or more, was taken to mean hypertension. There were 747 cases in which this required reading occurred. Male hearts which weighed 500 Gm. or more, and female hearts of 450 Gm. or more, in the absence of valve deformities or an adherent pericardium, were considered to be hypertensive hearts. In this group there were 149 cases (13.3 per cent of the myocardial in-

sufficiency group and 3 per cent of the total) in which the systolic pressure was known to have been below 150 mm. Hg, and 163 cases (14.5 per cent of the myocardial insufficiency group and 3.6 per cent of the total) in which the blood pressure was unknown. Hearts with hypertrophy in cases of glomerulonephritis were not included. There was a small group with heart weights below the above requirement (sixty-five cases, or 5.8 per cent of the cases of myocardial insufficiency and 1.3 per cent of the total). These patients had had cardiac dilatation and general congestive failure. Most of them had some degree of hypertrophy.

Age and Sex (Table V).—In the group of patients with myocardial insufficiency, the greatest number died in the seventh decade. A large majority of the deaths occurred in the fifth to ninth decades in both sexes. No deaths occurred in the first two decades among the males and in the first three decades among the females.

TABLE V

AGE AND SEX INCIDENCE IN TYPES OF HYPERTENSIVE HEART DISEASE (2,597 CASES)

DECADE	AUTOP- SIES	HYPER- TENSION I		HYPER- TENSION II		HYPER- TENSION III		HYPER- TENSION IV		TOTAL	
		NO.	M	NO.	M	NO.	M	NO.	M	NO.	M
Males (1,881 Cases)											
1	2,978	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2	645	0	0.0	0	0.0	0	0.0	2	3.1	2	3.1
3	1,324	6	4.5	1	7.5	3	2.3	1	0.7	11	8.3
4	2,052	27	13.2	12	5.8*	10	4.9	9	4.4*	58	28.3*
5	3,132	99	31.6	104	33.2*	37	11.8*	29	9.2	269	85.9*
6	3,439	218	63.4	190	55.2*	79	23.0	28	8.1	515	149.8*
7	3,350	234	69.8	263	75.5*	66	19.7	26	7.8	589	175.8*
8	2,172	173	79.6	135	62.1*	34	15.6	7	3.2	349	160.7
9	565	39	69.0	41	72.6*	3	5.4	3	5.3	86	152.2
10	28	2	71.4	0	0.0	0	0.0	0	0.0	2	71.4
Total	19,685	798	40.5*	746	37.9*	232	11.8	105	5.3	1,881	95.6*
Females (716 Cases)											
1	2,208	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
2	574	0	0.0	0	0.0	2	3.5	5	8.7	7	12.2
3	1,174	0	0.0	0	0.0	3	2.5	3	2.5	6	5.1
4	1,283	18	15.6	3	2.3*	10	7.8	18	14.0*	49	38.2*
5	1,347	39	28.7	6	4.4*	31	23.0*	18	13.5	94	69.8*
6	1,411	80	56.7	31	22.0*	30	21.2	12	8.5	153	108.4*
7	1,342	94	70.0	69	51.4*	31	23.1	7	5.2	201	149.8*
8	930	70	75.3	69	73.1*	15	16.1	6	6.4	160	172.0
9	279	25	89.4	11	39.4*	7	25.1	1	3.6	44	157.7
10	32	0	0.0	0	0.0	1	31.1	1	31.2	2	62.5
Total	10,580	326	30.8*	189	17.8*	130	12.3	71	6.7	716	67.7*

*A significant difference.

There was a significant sex difference in the total group of 1,124 cases (40.5 males and 30.8 females per thousand autopsies). No significant sex difference existed in any of the decades in this group.

2. *Coronary Sclerosis With Hypertension*.—The second group of cases of cardiac disease with hypertension were those in which death was due primarily to coronary sclerosis or to sclerosis and thrombosis. There were 935 cases (36 per cent of the hypertensive group and 20 per cent of the total).

On the basis of the evidence of hypertension, three groups of the cases of coronary disease were recognized: those in which there was a systolic blood pressure of 150 mm. Hg or more, 285 cases (30.5 per cent of the hypertensive coronary group and 6.1 per cent of the total); those in which the systolic blood pressure was below 150 mm. Hg, or the blood pressure was unknown, and in which the male heart weights were 500 Gm. or more, and the female, 450 Gm. or more, 290 cases (31 per cent of the hypertensive coronary cases and 6.2 per cent of the total); and those in which the systolic blood pressure was below 150 mm. Hg, or was unknown, and in which the male heart weights were 400 to 499 Gm., and the female, 350 to 449 Gm. Some in this third division may have been questionably hypertensive cases, but probably in most of them, especially those in which the heart weights were greater, there was a degree of hypertrophy most like that caused by hypertension. In this division of hypertensive coronary sclerosis there were 360 cases (38.5 per cent of the hypertensive coronary sclerosis cases and 7.6 per cent of the total).

Age and Sex (Table V).—The greatest number of males in the cases of hypertensive coronary sclerosis died in the seventh decade, and, of the females, in the seventh and eighth decades. The majority of the males were in the fifth to eighth decades and the females in the sixth to ninth decades. The males greatly outnumbered the females in the total number of 935 cases (37.9 males per thousand autopsies on males and 17.8 females per thousand autopsies on females). There was a significant male predominance in all the decades in which death occurred except in the third, in which there was only one death, a male. The greatest sex difference was in the fifth decade (33.2 males and 4.4 females per thousand autopsies).

3. *Encephalopathy (Apoplexy)*.—The third division of the hypertensive cases included those in which death was caused by cerebral hemorrhage. In most of these there were also evidences of cardiac failure, both clinically and at autopsy. Death evidently would probably have resulted from cardiac failure had life not been terminated by hemorrhage of the brain.

In this apoplectic group there were 362 cases (13.9 per cent of the hypertensive group and 7.7 per cent of the total). By our method of determining the presence of hypertension, this apoplectic group was divided into two subgroups. In the first (296 cases, or 81.8 per cent of the encephalopathy group and 6.3 per cent of the total) the recorded blood pressure was 150 mm. Hg or more. Those in the second, consisting

of sixty-six cases (18.2 per cent of the encephalopathy cases and 1.4 per cent of the total), were classed as hypertensive cases because the male hearts all weighed 500 Gm. or more, and the female hearts, 450 Gm. or more. It is probable that some cases of cerebral hemorrhage in which the blood pressure was less than 150 mm. Hg and the hearts weighed less than 500 Gm. in males and 450 Gm. in females should be included in this group, but they were not because it could not be determined with certainty that hypertension had existed.

Age and Sex (Table V).—The greatest number of males died in the sixth decade, and, of the females, in the fifth and seventh. A large majority of the deaths in both sexes occurred in the fifth to eighth decades. In the entire number there was no significant sex difference, but in the fifth decade there was a preponderance of females (11.8 males and 23 females per thousand autopsies).

4. *Renal Insufficiency.*—The fourth group of hypertensive cases was composed of those in which, although as a rule there were signs of cardiac failure, death was caused by uremia. Death would likely have been cardiac had uremia not intervened. In all of these there was a systolic blood pressure of 150 mm. Hg or more, or a male heart weight of at least 500 Gm. or a female heart weight of at least 450 Gm. There were 176 renal cases (6.8 per cent of the hypertensive group and 3.8 per cent of the total).

Age and Sex (Table V).—Most of the deaths in both sexes occurred in the fourth, fifth, sixth, and seventh decades. There were two males and five females in the second decade, and one male and three females in the third decade.

The sexes were about equal (5.3 males and 6.7 females per thousand autopsies). A significant sex difference was noted in one decade, the fourth, in which the females outnumbered the males (4.4 males and 14.0 females per thousand autopsies).

B. Coronary Sclerosis Without Hypertension.—The second group of noninfectious heart diseases was coronary sclerosis without hypertension. In all of these cases there was either a history of low blood pressure or the male hearts weighed less than 400 Gm., and the female hearts less than 350 Gm. There were 280 of these (9.5 per cent of the noninfectious cases and 6.2 per cent of the total). The total number of cases of coronary sclerosis in the entire cardiac group was 1,215. The 280 cases in which there was no hypertension constituted 23 per cent of the entire number of cases of coronary sclerosis. This indicates that in about 77 per cent of all cases of coronary sclerosis there is an associated hypertension.

Age and Sex (Table VI).—Most of the deaths in both sexes occurred in the fifth, sixth, seventh, and eighth decades. The males greatly outnumbered the females (12.6 males and 3 females per thousand

autopsies). In the entire group of cases of coronary sclerosis, with or without hypertension, the ratio of males to females was 2.5: 1 (males 50 per thousand and females 20 per thousand).

TABLE VI
AGE AND SEX INCIDENCE IN CORONARY SCLEROSIS WITHOUT
HYPERTENSION (280 CASES)

DECADE	MALES (248 CASES)			FEMALES (32 CASES)		
	AUTOPSIES	NO.	M	AUTOPSIES	NO.	M
1	2,978	0	0.0	2,208	0	0.0
2	645	0	0.0	574	0	0.0
3	1,324	4	3.0	1,174	0	0.0
4	2,052	18	8.8*	1,283	1	0.8*
5	3,132	51	16.3*	1,347	5	3.7*
6	3,439	65	18.9*	1,411	6	4.2*
7	3,350	53	15.8*	1,342	6	4.5*
8	2,172	39	17.9*	930	9	9.7*
9	565	16	28.3	279	5	17.9
10	28	2	71.4	32	0	0.0
Total	19,685	248	12.6*	10,580	32	3.0*

*A significant difference.

C. Pulmonary Hypertension.—Primary, right-sided heart failure as a result of increased pressure in the pulmonary artery is not an uncommon condition. There were sixty-nine cases (2.3 per cent of the noninfectious cardiac cases and 1.5 per cent of the total) in this series. The cause of primary, right-sided heart failure, or cor pulmonale, is not a specific one. In the sixty-nine cases the causal factors, listed in order of their frequency, were as follows: pulmonary tuberculosis (sixteen), bronchial asthma (fifteen), bronchiectasis (nine), pulmonary arteriosclerosis (nine), chest deformity (five), pulmonary embolism or thrombosis (five), emphysema (three), silicosis (two), pressure of a syphilitic aneurysm of the aorta upon the pulmonary artery (one), and nonspecific pulmonary fibrosis (one).

Age and Sex.—Thirty-nine of the forty-two males (92.8 per cent) and twenty of the twenty-seven females (74 per cent) died in the fourth to seventh decades. The sexes were about equal (2.1 males and 2.5 females per thousand autopsies).

D. Miscellaneous Group of Cases of Cardiac Failure.—There were few cases in this group. The thyroid heart, or cardiac death caused directly by the effects of hyperthyroidism or hypothyroidism upon the myocardium, was rare in our material. There were five cases in which the cardiac hypertrophy, dilatation, and congestive failure appeared definitely to be the result of hyperthyroidism. One patient with myxedema died of typical congestive heart failure.

The heart in cases of chronic glomerulonephritis regularly undergoes hypertrophy and dilatation, and clinically there is evidence of cardiac failure. The final cause of death, however, is uremia. We have had no cases of glomerulonephritis with congestive heart failure without uremia.

No case of beriberi heart, in so far as could be ascertained, was found among the more than 30,000 autopsies.

Cardiac hypertrophy and dilatation without hypertension, in the absence of valve deformity, still remains a much discussed and doubtful condition. It occurs congenitally in children and may possibly be found in the adult. It appears doubtful whether we have any such cases. The stigmata of hypertension were so common in those of our cases in which the blood pressure was not found to be elevated that we prefer to leave the question, "Is there an adult idiopathic cardiac hypertrophy and dilatation?" open for further study. All such cases in this analysis are included in the hypertensive group with myocardial insufficiency.

DISCUSSION

In a series of 30,265 autopsies there were 4,678 cardiac deaths (15.45 per cent). Etiologically, these were classed as cases of rheumatic, bacterial, syphilitic, hypertensive, arteriosclerotic (coronary), pulmonary hypertensive (cor pulmonale), and thyroid (hyper- and hypo-) heart disease.

The rheumatic group, 870 cases, comprised 18.6 per cent of the entire number of cases. Of these 870 cases, ninety-eight (11.3 per cent) were cases of acute rheumatic endocarditis, eighty-five (9.8 per cent) were cases of recurrent rheumatic endocarditis, and 650 (74.7 per cent) were cases of healed or nearly healed valve deformities; thirty-seven patients (4.2 per cent) died from the effects of an adherent pericardium.

The number of rheumatic cases in which death occurred during an acute attack was small. Patients with the calcific aortic valve deformity lived the longest. Acute rheumatic endocarditis is a disease primarily of young persons.

The sexes were almost equally represented in the rheumatic group, i.e., 25.6 males and 32.9 females per thousand autopsies. This was true only in the group as a whole. In the early decades the females predominated, and, in the later decades, the males were greatly in excess.

The 514 cases of bacterial endocarditis constituted 11 per cent of the entire cardiac group. In forty-nine of the 514 (9.5 per cent), the duration of symptoms was less than six weeks, and these were classed as cases of primary acute bacterial endocarditis. In 101 (19.6 per cent), the symptoms were the same as in the cases of primary acute endocarditis, but were secondary to some infection or wasting disease, and these cases were therefore classed as secondary acute bacterial endocarditis. In 364 of the 514 cases (70.8 per cent), the symptoms had lasted for more than six weeks, and these were classed as cases of subacute bacterial endocarditis.

In the combined group the greatest number of males died in the fifth decade, and the greatest number of females in the third. In the two

groups of acute endocarditis, the females predominated with a ratio of nearly 2:1. In the cases of subacute endocarditis the number was equal (twelve each per thousand autopsies). A factor in the sex difference in the cases of secondary acute endocarditis was the relatively large number of cases of abortion which were included. It is possible that among the cases of primary acute endocarditis there may have been some undetected abortions. The subacute endocarditis, as a rule, was caused by the *Streptococcus viridans*, whereas the organisms most frequently found in the acute cases were *Streptococcus hemolyticus* and *Staphylococcus aureus*.

There were 327 cases (7.0 per cent) of syphilitic cardiac disease in the entire series of 4,678 heart cases. In 180 (55 per cent), death occurred from aortic insufficiency; in seventy-four (22.6 per cent), from narrowing of the coronary orifices; in 68 (20.8 per cent), from rupture of an aortic aneurysm; and, in 5 (1.5 per cent), from gumma of the myocardium.

The majority of deaths occurred in the fourth, fifth, and sixth decades. The males predominated in the entire group, with a ratio of 2.8:1. The greatest preponderance of males was in the aortic insufficiency group (3.6:1).

Hypertension was by far the most frequent cause of cardiac disease. Of the total of 4,678, 2,597 (55.5 per cent) were hypertensive cases. In 1,124 (43.3 per cent) of these 2,597 cases, death was caused by myocardial insufficiency; in 935 (36 per cent) by coronary sclerosis; in 362 (13.9 per cent), by cerebral hemorrhage; and, in 176 (6.8 per cent), by renal insufficiency. In most cases, cardiac hypertrophy and dilatation were also present in the last two groups.

In all of the cases of hypertension, death occurred usually in the later decades, i.e., the fifth, sixth, seventh, eighth, and ninth. Males predominated among the patients who died of myocardial insufficiency (1.3:1) and coronary sclerosis (2.1:1). No significant sex difference was noted in the apoplectic and renal insufficiency groups.

There were 280 cases (9.5 per cent) of coronary sclerosis without hypertension. The total number of cases of coronary sclerosis with hypertension (935) and without hypertension (280) was 1,215 (25.9 per cent of all cardiac deaths). The males in the cases of coronary sclerosis without hypertension predominated with a greater ratio (4.2:1) than in those with hypertension.

Coronary sclerosis and the calcific nodular aortic valve deformity groups were the two outstanding divisions of heart disease in which there was a marked male preponderance. In the aortic stenosis group, this is explained by the fact that the aortic valve is involved more commonly in males than in females. The reason for the preponderance of males in the cases of death from coronary disease is not apparent.

Primary right-sided heart failure (cor pulmonale) was caused by a variety of conditions, and was distributed about equally between the two sexes.

Cardiac death from hyperthyroidism or hypothyroidism, without any other cardiac disease, was rare in this series of autopsies.

SUMMARY

A total of 4,678 cardiac deaths in a series of 30,265 autopsies (15.45 per cent) was analyzed. The incidence of the types, with the age and sex distribution, is given.

A classification of heart disease based upon etiology and autopsy observations is presented.

The statistical determinations were performed by Alice Marie Moeglein, M.S.

REFERENCE

1. White, P. D.: Heart Disease, New York, 1937, The Macmillan Co., p. 171.

THE NORMAL ELECTROCARDIOGRAM

I. ANALYSIS OF THE EXTREMITY DERIVATIONS FROM 100 NORMAL PERSONS WHOSE AGES RANGED FROM 30 TO 50 YEARS

KAJ LARSEN, M.D., COPENHAGEN, AND TH. SKÚLASON, M.D., REYKJAVÍK

UNTIL a few years ago, there was only one comprehensive work on the normal electrocardiogram, namely, that of Lewis and Gilder¹⁶ (1912), in which an account is given of the appearance of the extremity derivations from fifty-two normal men whose ages ranged from 18 to 35 years. It seems, however, as if it was realized in several quarters about simultaneously that a series of only fifty-two normal subjects is insufficient, in view of the present scope of clinical electrocardiography. The result was a number of studies on the normal electrocardiogram, among which the following may be mentioned: Jensen, Smith and Cardwright,¹¹ Gross,⁸ Hadorn,⁹ Shipley and Hallaran,²² Benedetti and Sabena,² Schulz,²¹ Chamberlain and Hay,³ Warnecke,²⁵ and Jenner, Hoskin, and Jonescu.¹⁰ In addition, several papers have been published on questions of details, some of which will be cited occasionally in the following.

When, notwithstanding the appearance of these modern studies, we believe we are still able to offer an additional contribution concerning the normal electrocardiogram, it is largely for the following two reasons. On going through the above-mentioned publications it is found that most of the experimental subjects were very young persons, or, in a couple of the studies, elderly, i.e., persons over 50, whereas the age class from 30 to 50 years is poorly represented. And we believe that this very age class is of particular interest, for it is between the ages of 30 and 50 years that the degenerative heart lesions commence to assert themselves. In the next place, it is found that, in contrast to Lewis and Gilder, the more modern investigators have given an insufficient account of the suitability of the apparatus for the tracing of the electrocardiogram. It is to be emphasized that, even though the employment of amplifiers means an advance, these apparatuses are encumbered with just as many possibilities of error as the string galvanometers, although of a different nature. From the following—under “Technique”—it will be evident how thoroughly and comprehensively the apparatus itself ought to be examined.

From the Medical Department B, the Rigshospital, Copenhagen.
Received for publication Feb. 10, 1941.

EXPERIMENTAL SUBJECTS

Our material comprised 100 normal persons whose ages were between 30 and 50 years; twenty-five men and twenty-five women were between 30 and 40, and 25 men and twenty-five women were between 40 and 50. The average ages for the four groups were 34.7, 35.0, 44.0, and 43.8 years, respectively. Of the women, forty-one were nurses in the Rigshospital, and nine were hospitalized patients. Of the men, seven were physicians, twenty-one were functionaries at the Rigshospital or similar institutions, and the rest were hospitalized patients. Of the patients here employed as "normal" subjects, seventeen were under treatment in Department B (lumbago-sciatica, seven patients; dyspepsia or gastroduodenitis, eight patients; omarthritis, one patient; sequelae of phlebitis, one patient), nine patients were in the Surgical Department C (fracture of the leg, four; hernia, two; lipoma, two; contusion of the face, one), and five patients were from Department H (eczema of slight degree, three; erythrasma, one; psoriasis of slight degree, one).*

All of the experimental subjects stated that they were able to stand physical exertion (work, sport) without having circulatory symptoms. None of them had ever had rheumatic diseases, but ten had had a mild attack of scarlet fever, and eight, a mild attack of diphtheria, many years earlier. Ordinary physical examination revealed no abnormality in any of them. As to their weight, most of them came very near the average given for their respective sex, age, and height in the weight tables of the Hafnia Insurance Co. In a couple of the cases the weight was 16 to 18 per cent above average. In all 100 subjects, roentgenographic examination of the chest showed that the heart was normal in shape and size, and that the lungs were normal. In all subjects the systolic blood pressure was less than 150 mm. mercury, and the diastolic, less than 100 mm. The sedimentation rate of the erythrocytes (in one hour) did not exceed 8 mm. for the men and 12 mm. for the women. The hemoglobin per cent was at least 85 (100 per cent = 18.5 volumes per cent of oxygen). The blood Wassermann reaction was negative on the hospitalized patients, and not done on the other subjects.

The subjects were selected solely on the basis of their anamnestic data. Because of the results of the objective examinations, a few subjects had to be excluded, namely, three for anemia, two for increased sedimentation rate, one for increased blood pressure, and two for adiposity. In the subject with increased blood pressure, the electrocardiogram showed left preponderance, and in one of the subjects with adiposity the electrocardiogram showed left preponderance and a QRS complex lasting 0.114 sec. In the other cases the electrocardiograms were normal. Finally, one subject, a nervous man, aged 32 years, was excluded because his heart rate during the tracing exceeded 100 per minute; in this case the S-T segment kept a level of 1 mm. below the isoelectric line in Leads II and S.

TECHNIQUE

The records were taken partly with derivation from the extremities, as used by Einthoven⁵ (Leads I, II, and III), partly with the precordial derivations used by Groedel⁷ (Leads *d* and *s*), and always with the subject in the reclining posture. The results of our studies on Leads *d* and *s* will appear in a subsequent paper.²³ The electrodes employed on the extremities, measuring about 70 sq. cm., were made of rust-proof steel, and covered with felt that was moistened in hot saline.

*We wish to acknowledge our indebtedness to the chiefs of Department C and Department H of the Rigshospital, Professor A. Lendorf and Professor H. Haxthausen, for permission to examine the patients from these departments. We likewise wish to give our best thanks to the chief of the X-Ray Clinic, Professor P. Flemming Møller, and his assistants, for the roentgenographic examination of our experimental subjects.

Most of the apparatus employed for the taking of the electrocardiogram was furnished by the Siemens and Halske A. G., and put together by Professor Warburg. In this apparatus the derived electrical potentials are amplified by two identical, four-stage, resistance-coupled amplifiers, with direct entrance to grid and earth, direct outlet to the oscillographic loops, and an entrance resistance of 1,000,000 ohms. With these amplifiers, Leads I and II are recorded simultaneously, and then Lead III is recorded with the same amplifier as Lead I. The tracing is made with bifilar oscillographic loops from Siemens and Halske A. G. The rate of movement of the photographic paper was 70 mm. per second. The time marking was done with a tuning fork and synchronizing motor from the Cambridge Scientific Instrument Co. Ltd., of London. On the shaft of the motor, which makes five revolutions per second, there is a disc with four slits, one of which is wider than the others, making the marked intervals 0.05 and 0.20 sec.

The suitability of the apparatus for the tracing of electrocardiograms was controlled frequently. The sensitivity of the amplifiers was controlled every day the apparatus was used; each derivation was supplied with a test pressure of 1 millivolt; the deflections for 1 mv. were about 20 mm. The capacity of the amplifiers for symmetrical tracing, true as to amplitude, and the accuracy of the timer were controlled about every twenty records. In all cases in which disproportionality and asymmetry gave rise to errors of more than 3 per cent in the height of the waves, corrections were made. The error from this source in the size of the various waves was, for waves up to 15 mm. in height (1.5 mv.), at the most, 0.5 mm.; and for waves up to 30 mm. in height, at the most, 1 mm. The timer was adjusted by tracing, on the film, the vibrations of a tuning-fork (a^1) which was checked in the Reichanstalt für physikalischen Messungen, Berlin, and found to have a period of 435 Hertz; the corrections, which were carried out invariably, never exceeded 2 per cent. Finally, through special tests, we have made sure that this apparatus, when it is used for electrocardiography, gives a record of the oscillations that is true as to frequency and phase. In making these tests, we ascertained the time constants of the two amplifiers, which, in both instances, were found to be 1.54 sec.; and, further, the damping constants and individual frequencies of the oscillographic loops were ascertained through analysis of individual charges sent directly through the loops. The latter examination, which was carried out by Professor Warburg, showed that the damping constants of the loops here employed were, respectively, 0.78 and 0.67, and that the individual frequencies of the two loops were, respectively, 870 and 820 Hertz.

In measuring the records, the isoelectric line was taken as a straight line that just touched the lower margin of the curve corresponding to the segments between the end of the U waves and the beginning of the P waves. The deviation of the P-Q segment from the isoelectric line was always measured at the point where the segment reached farthest down below, or farthest down towards, the isoelectric line. The deviation of the S-T segment from the isoelectric line was always measured at the point corresponding to 0.05 sec. after the end of the QRS complex. The size of the waves was measured from the inferior margin of the isoelectric line to the inferior margin of the curve at the apices of the waves. The measuring was done with calipers and a diagonal scale on six successive complexes in each derivation; the height of the waves was taken as the average of the six waves and converted to millivolts. The size of the waves was recorded in millimeters, so that 10 mm. = 1 mv., which is the form of recording most commonly employed. In repeated readings on the same wave, the error of the reading has not exceeded ± 0.2 mm. (corresponding to about ± 0.1 mm. in the tabulated results). The duration of the various intervals was measured by means of calipers, and the time registered on the record, and given in seconds. Here, too, the measuring was carried out on six successive complexes

in each derivation. Because of the rapid rate at which the photographic paper traveled, it was possible to read the times within 0.005 sec.; this figure gives also the numerical value of the reading error in repeated measurements of the same interval.

On measuring the electrocardiograms it was found that the size of the waves and the length of the intervals varied a little from one complex to another. Generally, this variation is assumed to be due chiefly to changes in the position of the heart resulting from the respiratory movements. In order to get an idea about the correctness of the values given for the size of the waves and the length of the intervals, it was necessary, therefore, to know the dispersion on these values. These dispersions were not calculated for the present material, but are known from previous work in which one of us (K. L.) took and measured electrocardiograms on twenty normal, younger persons with the same technique as described above. G. Rasch, Ph.D., calculated the dispersions for some of the more important values in Lead II, and found them to be 0.55 mm. for the R wave, 0.31 mm. for the T wave, 0.004 sec. for the P-Q interval, 0.003 sec. for the QRS complex, and 0.005 sec. for the Q-T interval. The aforementioned reading errors are included, of course, in these values for the dispersions. A review of the measuring results shows that the dispersions in Lead I must be of the same magnitude as in Lead II, whereas the dispersions for the R wave and the T wave in Lead III must be a little greater.

RESULTS

The results are summed up separately for each of the aforementioned four groups of experimental subjects. As there were only insignificant differences attributable to sex and age, the results of the total analysis of all 100 cases will be given first.

THE P WAVE

In Leads I and II the P wave was positive in all 100 subjects except one, in whom it was diphasic ($-0.5 + 0.5$ mm.) in Lead II. In Lead III there occurred positive, diphasic, and negative P waves (Table I). In Leads I and II the P wave had most often the form of a gradual curve, and was pointed but seldom. It was only in 10 per cent of the cases, however, that the curve was entirely smooth; 90 per cent of the records showed from one to four small notches (or small waves). This notching was rarely so pronounced that the P wave might properly be designated as bifid; this was found only five times in Lead II.

In Lead I the average height of the P wave was 1.0 mm., and in Lead II it was 1.3 mm. In these two leads no P wave was lower than 0.5 mm., and none higher than 2.5 mm. The highest P wave in the individual subject was found seventy-nine times in Lead II, twenty-four times in Lead I, and once in Lead III. (That the total incidence of this property in the three leads in these and similar data is not 100 per cent is due to the fact that in cases in which, for instance, the P wave was of the same height in two leads and higher in these than in the third lead, we have recorded the P wave as being highest in both of the two leads concerned.)

The average duration of the P wave was 0.10 sec.; the shortest P wave lasted 0.070 sec., and the longest, 0.133 sec. In the individual subject the difference in the duration of the P wave in the different leads was 0.04 sec. at the most; eighteen subjects showed a difference greater than 0.02 sec., and, in fifty-seven cases, the difference was greater than 0.01 sec. The longest P wave was found thirty-two times in Lead I, fifty-one times in Lead II, and thirty-one times in Lead III. In the electrocardiographic literature, as a rule, 0.10 sec. is given as the upper limit for the normal duration of the P wave. In eighty-two of our 100 subjects the P wave lasted 0.10 sec. or more in at least one lead, and in six subjects, even 0.12 sec. or more. According to our observations, therefore, the P wave may be said to be abnormally wide only in cases in which its duration is 0.14 sec. or more in at least one lead.

TABLE I
THE P WAVE

	LEAD		
	I	II	III
<i>Form</i> (no. of subjects)			
Positive	100	99	67
Diphasic	0	1	24
Negative	0	0	9
Smooth	12	10	10
Notches	88	90	90
Bifid	0	5	0
<i>Size</i> (mm.)			
Minimum	0.6	0.5	0.9
Maximum	1.9	2.1	1.7
Av.	1.0	1.3	
P wave largest (no. of subjects)	24	79	1
<i>Duration</i> (sec.)			
Minimum	0.074	0.083	0.070
Maximum	0.133	0.132	0.128
Av.	0.100	0.103	0.099
0.10 sec. or more (no. of subjects)	58	69	46
0.12 sec. or more (no. of subjects)	4	6	4
P wave longest (no. of subjects)	32	51	31

THE P-Q SEGMENT AND THE P-Q INTERVAL

The P-Q segment signifies the section of the curve from the end of the P wave to the beginning of the QRS complex, whereas the P-Q interval (conduction time) signifies the time from the beginning of the P wave to the beginning of the QRS complex. In about 95 per cent of the cases the course of the P-Q segment was horizontal; in the rest it was rising or going down (Table II). In Leads I and III the P-Q segment most often followed the isoelectric line. In Lead II the P-Q segment was below the isoelectric line in a little more than one-half of the cases; the P-Q segment took this course, also, fourteen times in Lead I and twenty-one times in Lead II. Further, in Lead III this segment was found above the isoelectric line in twelve cases. The maximal deviation from the isoelectric line in either direction was 0.5 mm.

The average duration of the P-Q interval was 0.163 sec.; the shortest duration was 0.107 sec., and the longest, 0.218 sec. In eight subjects the duration in one or more leads was 0.20 sec. or more; in two subjects the duration was over 0.21 sec., namely, 0.214 and 0.218 sec., respectively. In no subject was the duration of the P-Q interval simultaneously in all three leads less than 0.12 sec. In the present series the duration of the P-Q interval showed no relation to the pulse rate; but, of course, this does not exclude the possibility of such a relation in the individual person. Consequently, for "prolonged conduction time" we have to require that the duration of the P-Q interval be 0.22 sec. or more in at least one lead, and for "abnormally short conduction time" we have to demand a P-Q interval which lasts less than 0.12 sec. in all three leads. However, the conduction time may also be designated as prolonged in some cases in which the P-Q interval is less than 0.22 sec., namely, in those in which the conduction time is at least 0.02 sec. longer than it was in a previous electrocardiogram taken under the same conditions.

TABLE II
THE P-Q SEGMENT AND THE P-Q INTERVAL

	LEAD		
	I	II	III
<i>Course of P-Q segment</i> (no. of subjects)			
Horizontal	96	93	94
Rising	0	3	5
Falling	4	4	1
Isoelectric	86	46	67
Above isoelectric line	0	0	12
Below	14	54	21
<i>Duration of P-Q interval</i> (sec.)			
Minimum	0.112	0.121	0.107
Maximum	0.218	0.214	0.212
Av.	0.162	0.164	0.163
0.20 sec. or more (no. of subjects)	7	6	5
Less than 0.12 sec. (no. of subjects)	4	0	1
P-Q longest (no. of subjects)	35	47	40

The P-Q interval was longest in Lead I in thirty-five subjects, in Lead II in forty-seven, and in Lead III in forty. The greatest differences between the duration of this interval in the three leads in the individual subject were 0.05, 0.048, and 0.03 sec.; in nine subjects the difference was 0.02 sec. or more; in forty-nine subjects the difference was 0.01 sec. or more.

TABLE III
SIMULTANEOUS OCCURRENCE OF THE Q WAVE OR THE S WAVE IN THE DIFFERENT LEADS

WAVE	LEADS							NONE
	I-II-III	I-II	I-III	II-III	I	II	III	
Q	28	28	0	15	27	0	0	2
S	48	11	0	20	10	0	7	4

THE QRS COMPLEX

Form.—Most often the QRS complex was diphasic or triphasic; only in rare instances did it consist of a single wave, and, then, always of the R wave. Such a monophasic QRS complex occurred only two times in Lead I, seven times in Lead II, and six times in Lead III. The frequency of the Q and S waves is given in Table V, and Table III shows

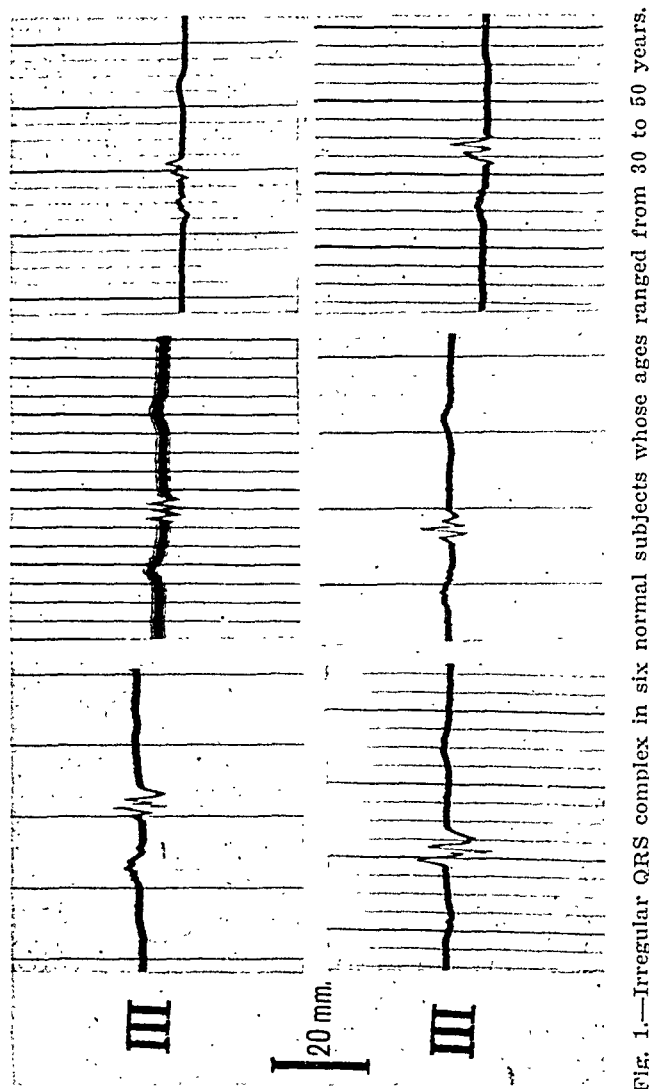


FIG. 1.—Irregular QRS complex in six normal subjects whose ages ranged from 30 to 50 years.

how often Q waves or S waves were found simultaneously in two or three leads. It will be noticed that neither the Q wave nor the S wave was ever found simultaneously in Leads I and III without being present in Lead II, and also that these waves never occurred in Lead II alone. This is in keeping with Einthoven's equation, namely, Lead II - Lead I = Lead III.

In some of the cases the QRS complex in Lead III was very irregular, with as many as three positive and negative waves, besides additional

nodules and notching. Some examples of such irregular complexes are shown in Fig. 1. In some cases the QRS complex was more than triphasic in Leads I and II, also, and the S wave was followed by a small positive wave. This wave has no designation in Einthoven's nomenclature, and hence it is sometimes designated as "innominate"; it occurred eleven times in Lead I, twelve times in Lead II, and eighteen times in Lead III. In Lead III this wave is known clinically as "the second positive R wave of Lead III," and diagnostic significance has been attached to its presence. For this reason it will be mentioned again in the last paragraph of this section.

Here mention is to be made also of the occurrence of nodules (punctate thickening) and notching of the waves. In order to avoid mistakes, we have to demand that the deformity must turn up again and again in a number of complexes. Still, the location of the deformities may vary a little; further, a deformity may turn up in some complexes as a nodule and in the following complexes appear as a slight notching. These variations are attributed to changes in the position of the heart caused by the respiratory movements. We have found it convenient to apply the designation *basal* to the nodules and notches located in that quarter of the waves that is nearest the isoelectric line, and deformities outside this part are designated as *apical*.

TABLE IV
OCCURRENCE OF NODULES AND NOTCHING ON THE R, Q, AND S WAVES

WAVE	DEFORMITIES	LEADS							
		I-II-III	I-II	I-III	II-III	I	II	III	NONE
R	Apical	20	1	8	14	13	5	21	18
R	Apical + basal	36	1	15	17	6	4	16	5
Q	Apical + basal	0	0	0	3	1	1	12	83
S	Apical + basal	5	4	2	18	7	4	19	41

From Table IV it is evident that nodules and notching are very common deformities of the R wave, but less frequent on the S wave, and particularly infrequent on the Q wave. The latter fact is due to the circumstance that the Q and S waves are absent in several derivations, and very small in others. Apical deformities on the R wave were found in twenty subjects simultaneously in all three leads, in twenty-three subjects simultaneously in at least two leads, and in thirty-nine subjects in only one lead; they were absent in all leads in eighteen subjects. Taking the apical and basal deformities together, they were present in thirty-six subjects simultaneously in all three leads, and in only five subjects was the R wave smooth in all three leads. In these five subjects, however, the Q wave or the S wave showed some notching or nodules, so that the QRS complex in no instance was free from these deformities simultaneously in all three leads.

After these observations, we are not able, like some clinicians, to attach any diagnostic significance to these deformities. It may be that notching of a certain degree is of some importance. On going through our records, we find, for instance, that in no case did the R wave in Leads I and II show apical notches in which the shortest limb measured more than 1 mm., or in which the shortest limb was longer than one-sixth of the height of the wave. But further investigation of this point is required.

Size and Duration.—The average size of the R wave was 7.7 mm. in Lead I, 10.2 mm. in Lead II, and 4.6 mm. in Lead III (Table V). In thirty subjects the R wave was highest in Lead I, in seventy subjects in Lead II, and in two subjects in Lead III. In fifteen subjects the R wave in Lead I was less than 5 mm. high; the same was the case in two subjects in Lead II, and in fifty-nine subjects in Lead III. On the other hand, in no instance did all three derivations from the same subject show an R wave less than 5 mm. in height; in other words, in this series no instance of "low voltage" occurred.

TABLE V
THE QRS COMPLEX

	LEAD		
	I	II	III
<i>R wave</i> (size in mm.)			
Minimum	1.8	4.1	0.7
Maximum	12.4	23.4	20.8
Av.	7.7	10.2	4.6
Less than 5 mm. (no. of subjects)	15	2	59
R wave largest (no. of subjects)	30	70	2
<i>Q wave</i> (size in mm.)			
Maximum	5.1	4.4	3.9
Av.*	0.7	0.9	1.1
Present (no. of subjects)	83	70	42
<i>S wave</i> (size in mm.)			
Maximum	5.4	5.8	7.6
Av.*	1.5	1.9	2.6
Present (no. of subjects)	72	79	74
<i>Duration of QRS complex</i> (sec.)			
Minimum	0.065	0.067	0.065
Maximum	0.108	0.118	0.121
Av.	0.084	0.087	0.088
0.08 sec. or more (no. of subjects)	62	69	70
0.10 sec. or more (no. of subjects)	4	12	12
QRS longest (no. of subjects)	26	42	52

*These averages are calculated per number of waves present.

Calculation of the dispersions on the size of the R wave showed that the dispersion was ± 2.2 mm. in Lead I, ± 3.1 mm. in Lead II, and ± 3.4 mm. in Lead III. Taking the triple values of the dispersions as sufficiently safe limits for the normal variation in the size of the R wave, we may then characterize the R wave as abnormally high when it measures 20 mm. or more in Lead II, and 15 mm. in Leads I and III. In three of our subjects the height of the R wave fell outside these limits, namely,

in Case 83, in Leads II and III ($R_2 = 23.4$ mm., $R_3 = 20.8$ mm.), and in Cases 44 and 61 in Lead III (R_3 , respectively, 15.4 and 16.7 mm.). The diagnostic significance of an abnormally high R wave is yet unsettled and has to be investigated on clinical material; among others, there is the question whether the R wave has to be abnormally high in all three leads in order to be of significance, or perhaps merely in one or two leads.

The Q wave was present twice as often in Lead I as in Lead III, whereas the occurrence of the S wave was about equally frequent in all three leads. From the average values it will be noticed that the Q wave in many cases was small.

In the three leads the average duration of the QRS complex varied between 0.084 and 0.088 sec. The difference in the duration of QRS in the different leads in the individual subjects was greater than 0.01 sec. in twenty-eight cases, and greater than 0.02 sec. in six cases; its maximum was 0.029 sec. The QRS complex was longest in Lead I in twenty-six subjects, in Lead II in forty-two, and in Lead III in fifty-two. The shortest measured duration was 0.065 sec., the longest, 0.121 sec. In eighty subjects the duration was 0.08 sec. or more in at least one lead, and in fourteen subjects it was 0.10 sec. or more. In the literature, 0.10 sec. is given as the upper limit for the normal duration of the QRS complex.¹⁸ In order to make the diagnosis of intraventricular block,¹⁸ the duration of the QRS complex has to exceed 0.12 sec.; a QRS complex lasting 0.10 to 0.12 sec. is characterized as "prolonged," with the addition that "such records are regarded by some as instances of incomplete bundle branch block." According to our observations, QRS complexes lasting from 0.10 to 0.12 sec. have to be looked upon as normal (for the age classes here examined), and the diagnosis of intraventricular block requires a QRS complex of more than 0.12 second's duration.

Left and Right Preponderance.—The question of preponderance is difficult to deal with because of the prevailing uncertainty as to which records show preponderance, and what these changes signify. In a subsequent work we hope we shall be able to return to these problems, and hence we shall here limit ourselves to a few brief remarks.

As is well known, for every point in the QRS complex it is possible to calculate and plot the angle for the electric axis and the value for the electrical potential when we know the potentials corresponding to the point in at least two derivations. Corresponding to the QRS complex, the end point of this vector follows a curve (vector diagram) of more or less irregular form. If this curve falls exclusively within the quadrant, with the angles from 0 to $+90^\circ$ (right lower quadrant), preponderance is out of the question. If, on the other hand, the greater part of the curve falls within the quadrant with the angles from 0 to -90° (right upper quadrant), there is preponderance of the left side of the heart; and, if the greater part of the curve falls within the quadrant with the

angles from $+90^\circ$ to $+180^\circ$ (left lower quadrant), there is right preponderance. One of the difficulties consists in giving simple rules to show which records correspond to the vector diagrams described. From theoretical studies, one of us (K. L.) has set up the following rules: *For right preponderance it is required that the S wave in Lead I exceed the R wave in the same derivation as to size and duration. For left preponderance it is required that the S wave in Lead III exceed the R wave in the same derivation as to size and duration, and also that it be greater than one-half of the R wave in Lead I.* After some preliminary studies¹⁵ these rules appear to function satisfactorily; but they are not applicable to cases in which the QRS complex is markedly diphasic in all three derivations.

As we are not in possession of vector diagrams from our 100 subjects, we have analyzed the electrocardiograms according to the rules given above. We found left preponderance in five cases, namely, in two men (aged 35 and 41) and three women (aged 45, 46, and 47). In two of these subjects the body weight was above the normal average; on the other hand in neither case did the roentgenograms show any pronounced transverse position of the heart. In eighteen other subjects the S wave in Lead III was greater than the R wave, without being half as great as the R wave in Lead I. The greater part of the vector diagram corresponding to such a record will fall within the space between 0° and $+30^\circ$, and hence the record may be designated as showing a tendency toward left preponderance. Of these eighteen subjects, twelve were men, and eight of these men were over 40 years old; all of the six women were over 40 years of age. Therefore, left preponderance and a tendency toward it were considerably more frequent in the age class of 40 to 50 years than in the age class of 30 to 40 years. In nine of these eighteen subjects the weight was above the normal average.

There was no instance of right preponderance, but in two cases the record was "right sided," i.e., the S wave in Lead I was approximately equal to the R wave. Both of these subjects were thin young men (aged 30 and 31), with wide chests.

Other Aspects of the QRS Complex.—No large Q_3 ¹⁹ was observed in this series. On the other hand, in some of the cases the Q wave in Leads I and II exceeded the limits given by Kossmann, Shearer, and Texon¹³ for the normal absolute and relative sizes of the Q wave, for Q_1 in two cases was greater than 2 mm., and in five cases greater than 15 per cent of the highest wave in all three derivations; and, in one case, Q_2 was greater than 20 per cent of the highest wave in all three derivations.

"M" or "W" complexes⁴ were not encountered in Leads I and II, but they were seen in Lead III, where they are of no significance.

QRS complexes of the forms described by Proger and Minnich²⁰ (left preponderance with positive T_2 and $T_3 > T_1$ and/or $S_2 > \frac{1}{2} R_2$

and/or $T_1 < \frac{1}{7} R_1$) were encountered twice. Case 64 (a woman, aged 47) showed left preponderance, a positive T_3 , and an S wave in Lead II that was greater than one-half of R_2 ; and Case 92 (a woman, aged 46) showed left preponderance, a positive T_3 , and a T wave in Lead I that was smaller than $\frac{1}{7}$ of R_1 .

As mentioned before, eighteen of our subjects showed, in Lead III, an additional positive wave after the R wave. In nine of these eighteen subjects the QRS complex in Lead III met the criteria set up by Katz and Slater¹² for "the second positive R wave of the QRS complex," for here the second positive wave occurred in records with left preponderance, or a tendency toward it; in six of the cases the second positive wave was greater than the first. Of these nine subjects, five were men (aged, respectively, 35, 35, 39, 46, and 47) and four, women (aged 41, 45, 46, and 47).

THE S-T SEGMENT

In Leads I and II the S-T segment proceeded most often obliquely upward (Table VI) because of the fact that in these derivations the T wave was always positive. In Lead III the segment was most often horizontal because of the diphasic, isoelectric, and negative T waves which occurred in this derivation. Saddle-shaped S-T segments¹⁷ were seen in twenty-two subjects, in whom they occurred fourteen times in Lead I, thirteen times in Lead II, and four times in Lead III. In eighteen cases the saddle form was associated with the presence of an additional positive wave in the QRS complex; in the remaining thirteen cases the S wave was absent. On account of the frequent occurrence of a saddle-shaped S-T segment in a series like the present, we are not able to attach any great diagnostic importance to this change. Further investigation of this question is planned.

TABLE VI
THE S-T SEGMENT

	LEAD		
	I	II	III
<i>Course</i>			
Horizontal (no. of subjects)	12	12	63
Rising (no. of subjects)	74	75	17
Falling (no. of subjects)	0	0	16
Saddle-shaped (no. of subjects)	14	13	4
Isoelectric (no. of subjects)	40	36	47
Above isoelectric line (no. of subjects)	46	44	38
Maximal elevation (mm.)	1.3	0.9	1.2
Below isoelectric line (no. of subjects)	14	20	15
Maximal depression (mm.)	0.3	0.5	0.6

Deviations of the S-T segment from the isoelectric line, as mentioned, were always measured 0.05 sec. after the end of the QRS complex. This is expedient, for in this way we avoid designating as abnormally negative those S-T segments that fall more than 1 mm. under the isoelectric

line only just after their start from the QRS complex. The frequency of an isoelectric level and elevation and depression of the S-T segment in the various derivations is evident from Table VI—likewise, the maximal deviations of the S-T segment from the isoelectric line in either direction. In no instance did the S-T depression exceed 1 mm., and in no instance was the S-T elevation 1.5 mm. or more. Therefore, S-T segments showing such deviations will be designated as abnormal. It is to be added, however, that, in our estimation, no particular significance is to be attached to elevations of the S-T segment above 1.5 mm. if the form of the segment and the following T wave are normal.

In practice, the isoelectric line is often established as a horizontal line through the P-Q segment, especially in cases in which, because of a rapid heart beat, there is no horizontal segment between the end of the T wave and the beginning of the P wave. When there was an auricular T wave,²⁴ however, several subjects showed a depression of the P-Q interval. Then the question is how much the S-T segment has to deviate from the P-Q segment in order to be designated as abnormally negative. According to our observations, the requirement is that the S-T segment in Leads I and II, when there is no positive deflection of the P-Q segment (Table II), must be 1 mm. or more below the level of the P-Q segment; and in Lead III, in which the P-Q level may be as much as 0.5 mm. over the isoelectric line, the S-T segment must lie 1.5 mm. or more below the P-Q level. This means that we shall be unable to make a diagnosis of an abnormally negative S-T segment in several of those cases in which the S-T segment in Leads I and II was 1 to 1.5 mm. below the isoelectric line proper (in Lead III, 1 to 2 mm. below the isoelectric line), and in which the P-Q segment also was negative, but, as far as we can see, this cannot be helped.

THE T WAVE

In Leads I and II the T wave was positive in all 100 subjects; in Lead III it was positive in fifty-eight subjects, diphasic in twenty-five, isoelectric in six, and negative in eleven. The curve of the T wave was always quite smooth, i.e., free from the small notches that are so common in the P, R, and S waves.

In Lead I the average size of the T wave was 2.6 mm., and, in Lead II, 3.0 mm. In forty records the T wave was largest in Lead I, in sixty-two it was largest in Lead II, and in no instance was it largest in Lead III. In three of the subjects the height of the T wave in Lead I was less than 1 mm. In Lead II, on the other hand, the T wave was in no instance less than 1 mm. Therefore, in the present series there was no instance in which the T wave was less than 1 mm. in all three derivations. On calculation, the dispersion for the T wave in Lead I was found to be ± 0.96 mm.; and in Lead II it was ± 1.10 mm. If, as usual, we take the triple values for the dispersions as sufficiently safe limits for the normal

variations in the size of the T wave, we find that a T_1 of 6 mm. or more and a T_2 of 6.5 mm. (in practice, 7 mm., or more) may be designated as abnormally high. In our series these limits were exceeded only once, namely, in Case 80 (man, aged 39), whose T wave in Lead I was 6.5 mm. in height.

TABLE VII
THE T WAVE

	LEAD		
	I	II	III
<i>Form</i>			
Positive (no. of subjects)	100	100	58
Diphasic (no. of subjects)	0	0	25
Isoelectric (no. of subjects)	0	0	6
Negative (no. of subjects)	0	0	11
<i>Size (mm.)</i>			
Minimum	0.7	1.1	1.9
Maximum	6.5	5.8	4.3
Av.	2.6	3.0	
Less than 1 mm. (no. of subjects)	3	0	
T wave largest (no. of subjects)	40	62	0

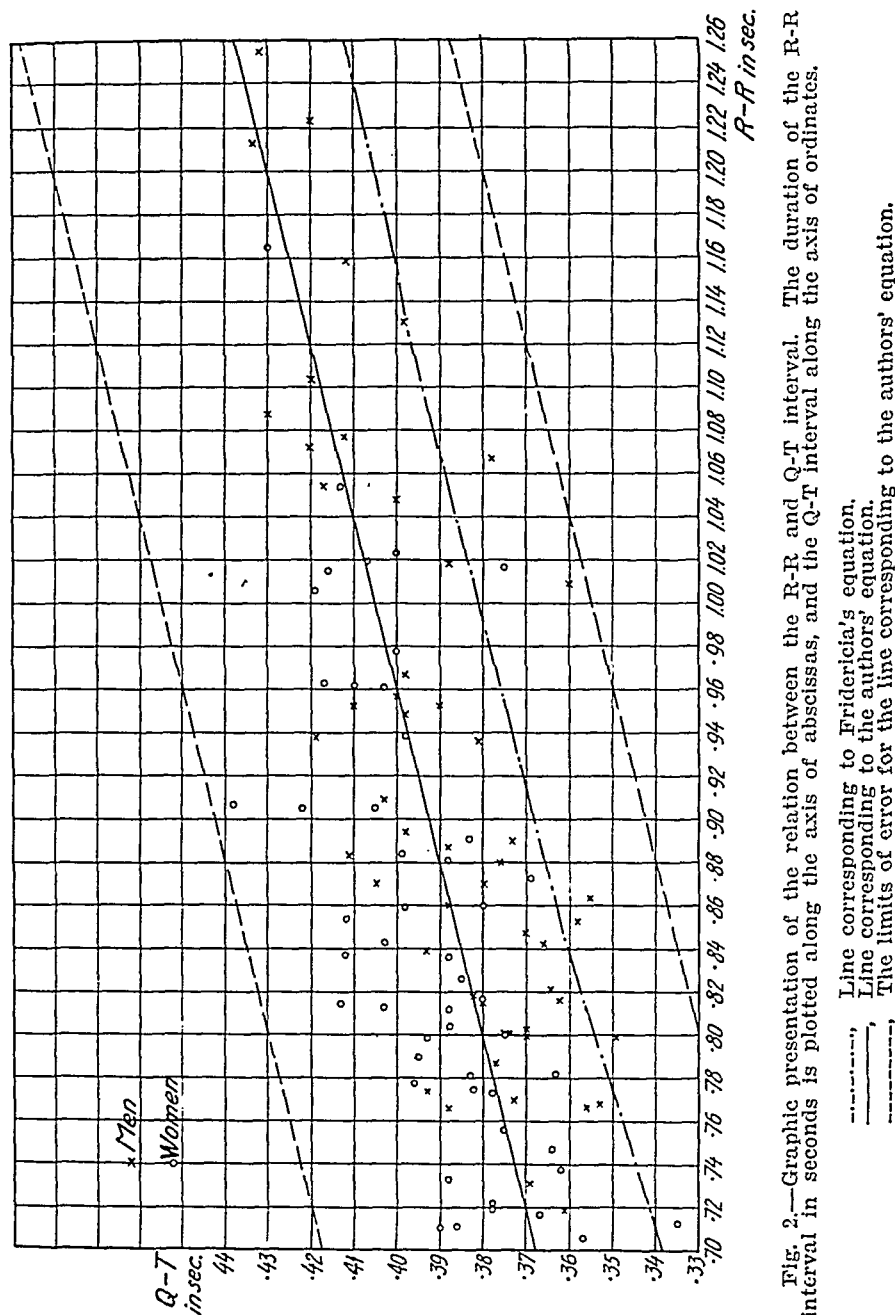
In Lead III the largest negative T wave measured 1.9 mm. Of the two largest diphasic T waves, the negative phase measured respectively 1.2 and 1.1 mm., and the positive phase, 0.5 and 0.8 mm. In the other cases both phases measured less than 1 mm.

THE Q-T INTERVAL

Data on the duration of the Q-T interval are of significance only in connection with data on the average duration of the R-R interval, i.e., the pulse rate, because the duration of the Q-T interval is largely dependent upon the rate of the heartbeat. For this relation, formulas of different types have been devised; the best known are the one given by Bazett,¹ in 1920, namely, $\text{systole} = K \times \sqrt{\text{cycle}}$, in which Bazett found K to be 0.37 for men and 0.40 for women, and that given by Fridericia,⁶ likewise in 1920, namely, $Q-T = 8.22\sqrt[3]{R-R}$. In Fridericia's equation the constants were ascertained from the examination of fifty normal persons of both sexes, whose ages ranged from 2 to 81 years; the limit of experimental error was found to be ± 0.045 sec.

The results of our study are recorded in Fig. 2, in which the duration of the R-R interval in seconds is plotted along the axis of abscissas, and the duration of the Q-T interval in seconds is plotted along the ordinate. The curve corresponding to Fridericia's equation is inserted in the figure. It will be noticed that the distribution of our data is uneven; in ninety-three of the cases the figures fell above Fridericia's curve, and below in only seven. The cause of this must be an error in the method. Since we were unable to find such an error in our study, we turned to

Fridericia's report, and noticed in particular that, even though Fridericia calls attention to the importance of an accurate timer, he fails to state whether his timer was adjusted, and how. On further investigation it was found that Fridericia's timer must have been running about



10 per cent too slow in order to be able to cause all the difference between his results and ours. And, in our opinion, an error of 10 per cent in the measuring of such short periods as those concerned here is not large enough to attract attention without regular and systematic adjustment.

Instead of correcting Fridericia's equation according to our results, we have done something else. A glance at Fig. 2 shows that the curvature of Fridericia's curve in the field of frequency with which we are concerned (48-85) is so slight that the curve may readily be replaced by a straight line. The equation for this line must be the formula $Y = a \cdot x + b$. We have ascertained the constants by graphic plotting, and arrived at the following result:

$$Q-T = 0.125 \times R-R + 0.28 \text{ sec.}$$

In this equation Q-T and R-R are given in seconds. Although this equation was obtained graphically, it is fully satisfactory for our data, as is evident from the fact that, in our 100 cases, the standard deviation from the line corresponding to this equation was -0.00052 sec. , i.e., very insignificant.

The mean error (m) of the individual deviation (A) may be calculated from the formula $m = \pm \sqrt{\frac{\sum A^2}{n-2}}$ in which n is the number of observations, and is found to be $\pm 0.0164 \text{ sec.}$ Therefore, the actual limit of error is ± 0.0492 , or, practically, $\pm 0.05 \text{ sec.}$ Both the lines corresponding to the obtained equation and those corresponding to the limits of error are plotted in Fig. 2, and it will be noticed that, in all our 100 cases, the figures fell within the field marked off in this way.

The obtained equation may be written as follows:

$$Q-T = \frac{1}{8} R-R + 0.28 \pm 0.05 \text{ sec.}$$

In this form the equation is so easy to remember and employ that the examiner at the bedside may readily decide whether or not the Q-T interval is of normal duration, without the use of tables or other adjuvants.

It is worth while, we believe, to look into the question whether there is any difference in the duration of the Q-T interval in the two sexes. The studies reported by Bazett were suggestive of such a difference, and further analysis of Fig. 2 shows that in a majority of our female subjects the Q-T interval had a positive deviation from the mean line, whereas the Q-T interval in a majority of the male subjects showed a negative deviation. The average deviation for the fifty women was $+0.0088 \text{ sec.}$, and for the fifty men it was -0.0098 sec. , which suggests that the Q-T interval is of longer duration in women than in men, but the total difference between the women and men was 0.0176 sec. , and this is so small in proportion to the mean error of the deviations in the two groups that it is not significant statistically. It will require a considerably greater number of observations to settle the question of a possible sex difference.*

*Dr. Jorgen Frost has called our attention to the fact that Adams and Sebastiani previously have derived formulas of the same type as ours for the relation between the Q-T and R-R intervals. Adams' formula (J. Clin. Investigation 15: 335, 1936) is $Q-T = 0.1464 R-R + 0.2572 \text{ sec.}$, and gives values for Q-T which, with rates from 40 to 90, are only 4.3 to 1 per cent below the values calculated from our formula. The formula of Sebastiani (Arch. d. mal. du coeur 31: 973, 1938) is $Q-T = \frac{1}{10} R-R + 22.2 \text{ sec.}$, and gives an all-too-short duration of the Q-T interval.

THE U WAVE

The U wave always had the form of a low, smooth, upward, convex—i.e., positive—curve. No negative U wave was observed. Our subjects' heart rates were such that the U wave was always free of the T as well as the P wave. In Lead I the U wave was visible in fifty-seven subjects, in Lead II in eighty-three, and in Lead III in forty. In fifteen subjects the U wave could not be seen in any of the three derivations.

ARRHYTHMIAS

Distinct respiratory arrhythmia, i.e., variations in the R-R interval of 0.10 sec. or more, occurred in twenty-four subjects, thirteen of whom were women, and eleven, men.

One man, aged 45, showed a single ventricular extrasystole. None of the subjects had any sensation of extrasystoles.

Other arrhythmias were not encountered.

SEX AND AGE DIFFERENCES

All the features of the electrocardiogram mentioned in the preceding sections were examined with a view to ascertaining whether there were sex and age differences. In all positive and doubtful cases we have ascertained whether the difference between the two averages was greater or smaller than three times the value of the mean error of the difference (m_D). As is well known, the formula for m_D is $m_D = \sqrt{m_A^2 + m_B^2}$, in which m_A and m_B are the mean error of the two averages. The results are given in Table VIII, in which the statistically significant differences are shown in italics.

TABLE VIII
SEX AND AGE DIFFERENCES

	MEN	WOMEN	30-40 YEARS	40-50 YEARS
<i>Av. height of waves (mm.) (Lead II)</i>				
P wave	1.3	1.3	1.3	1.3
R wave	10.8	9.6	10.5	9.9
T wave	3.4	2.7	3.0	3.1
<i>Av. duration (sec.) (Lead II)</i>				
P wave	0.106	0.101	0.102	0.105
P-Q interval	0.168	0.160	0.163	0.165
QRS complex	0.092	0.083	0.088	0.086
<i>Other components (no. of subjects)</i>				
P-Q positive in Lead III	1	11	8	4
S-T positive in Lead I	34	12	26	20
S-T positive in Lead II	30	14	23	21
Saddle-shaped S-T	10	12	5	17
Left preponderance and "lefty"	14	9	5	18
"Second positive R _{III} "	5	4	3	6
Respiratory arrhythmia	11	13	16	8

As is evident from Table VIII, the waves on an average are higher in men than in women, and the average durations of the P wave, P-Q

interval, and QRS complex are a little longer in men than in women. As mentioned before, the opposite applies to the Q-T interval, which on an average is a little longer in women than in men. The difference is too small, however, to be statistically significant. To settle the question of a possible sex difference, which might perhaps be due solely to a difference in the size of the bodies, a considerably larger series of cases would be required. In the two age classes here considered (persons between 30 and 40 years, and between 40 and 50 years), the mentioned components showed only insignificant differences.

In the present series the only definite sex difference was in the form of the P-Q and S-T segments. In Lead III the P-Q level was more often above the isoelectric line in women than in men, and in Leads I and II the S-T level was more often above the isoelectric line in men than in women. These features are of no significance in clinical electrocardiography.

The two age groups showed a statistically significant difference in the frequency of occurrence of a saddle-shaped S-T segment and left preponderance; both changes were more frequent in the older subjects. The same applies to the occurrence of the second R wave in Lead III, whereas respiratory arrhythmia was more common in the younger subjects; but these two differences were not statistically important.

CORRELATIONS

The correlations between the components of the electrocardiogram were studied by means of graphic presentations, and, in doubtful cases, by calculation of the coefficient of correlation (r). Between the duration of the R-R interval (pulse rate) and the other components in Lead II the correlations given in Table IX were found to exist.

TABLE IX

R-R interval and height of the P wave	No correlation (diagram)
R-R interval and duration of the P wave	No correlation (diagram)
R-R interval and P-Q interval	$r = +0.23 \pm 0.095$
R-R interval and height of the R wave	$r = -0.06 \pm 0.10$
R-R interval and duration of QRS	$r = +0.31 \pm 0.090$
R-R interval and height of the T wave	$r = +0.42 \pm 0.082$
R-R interval and Q-T interval	$r = +0.69 \pm 0.052$

As was to be expected, this analysis shows that there is a definite positive correlation between the R-R interval and the Q-T interval, and, further, that there are statistically significant, although slight, positive correlations between the R-R interval and the duration of QRS, and between the R-R interval and the height of the T wave. These observations mean that protracted QRS complexes and high T waves are more frequent in persons who at rest have a slow pulse rate than in persons who at rest have a more rapid pulse rate. Further, it will be noticed that r , on the whole, is increasing in the sequence given

above. This means that those components of the electrocardiogram that are caused by contraction of the myocardium are more dependant upon the pulse rate, in contrast to, or in a higher degree than are, the components caused by propagation of the impulse.

For other pairs of components in Lead II the correlations given in Table X were found.

TABLE X

Height of P and duration of P	No correlation (diagram)
Height of R and height of P	No correlation (diagram)
Height of R and duration of QRS	No correlation (diagram)
Height of R and height of T	$r = +0.30 \pm 0.094$
Height of T and duration of Q-T	$r = +0.24 \pm 0.094$

Thus, there was a very slight positive correlation between high R waves and high T waves, but no definite correlation, or no correlation at all, in the other cases.

In discussing the slight sex differences that are evident in Table VIII, we suggested that they might possibly be due merely to a difference between the size of the male and female body. Taking the surface area as a measure of body size, we found that the fifty women had an average surface of 1.70 sq.m., and the fifty men an average surface of 1.86 sq.m. We then studied the correlation between body surface and the two components of the electrocardiogram that show the greatest sex difference (Table XI).

TABLE XI

Body surface and height of R_2	$r = +0.03 \pm 0.10$
Body surface and duration of QRS ₂	$r = +0.31 \pm 0.09$

The statistically significant, positive, but slight, correlation between the body surface and the duration of the QRS complex lends support to the assumption set forth, at any rate as far as this component is concerned.

SUMMARY

The present work is an analysis of the extremity derivations from 100 normal persons (fifty women and fifty men) whose ages ranged from 30 to 50 years. After a thorough account of the experimental subjects, the electrocardiographic apparatus, and the technique employed in measuring of the electrocardiograms, the results are reported. Essentially, these results are evident from the tabulations.

REFERENCES

1. Bazett, H. C.: *Heart* 7: 353, 1920.
2. Benedetti, P. and Sabena, V.: *Arch. di pat. e clin. med.* 17: 491, 1938 (cited after *Zentralbl. f. d. ges. inn. Med.* 97: 128, 1938).
3. Chamberlain, E. N., and Hay, J. D.: *Brit. Heart J.* 1: 105, 1939.
4. Edeiken, J., and Wolferth, C. C.: *Am. J. M. Sc.* 188: 842, 1934.

5. Einthoven, W.: *Pflüger's Arch. f. d. ges. Physiol.* 122: 517, 1908.
6. Fridericia, L. S.: *Acta med. Scandinav.* 53: 469, 1920.
7. Groedel, F. M.: *Das Extremitäten-, Thorax- und Partial-Elektrokardiogramm des Menschen*, Dresden, 1934, Th. Steinkopff.
8. Gross, K.: *Ztschr. f. Kreislaufforsch.* 26: 545, 1934.
9. Hadorn, W.: *Ibid.* 27: 545, 1935.
10. Jenner, Hoskin, and Jonescu, P.: *Brit. Heart J.* 2: 33, 1940.
11. Jensen, J., Smith, M., and Cardwright, E. D.: *AM. HEART J.* 7: 718, 1932.
12. Katz, M. S., and Slater, S. R.: *Arch. Int. Med.* 55: 86, 1935.
13. Kossmann, C. E., Shearer, M., and Texon, M.: *AM. HEART J.* 11: 346, 1936.
14. Larsen, Kaj: *Om Forandringer i Elektrokardiogrammet hos Sunde og Syge under experimentel Iltmangel*. Dissertation. Copenhagen, 1938, Ejnar Munksgaard.
15. Larsen, Kaj, and Frost, J.: (To be published.)
16. Lewis, Th., and Gilder, M. D.: *Phil. Tr. Roy. Soc. London* 202B: 351, 1912.
17. Van Nieuwenhuizen, C. L. C., Hartog, H. A. Ph., and Matthijssen, E.: *Acta med. Scandinav.* 98: 468, 1939.
18. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart*, ed. 4, New York, 1939, New York Heart Association.
19. Pardee, H. E. B.: *Arch. Int. Med.* 46: 470, 1930 (II).
20. Proger, S. H., and Minnich, W. R.: *Am. J. M. Sc.* 189: 674, 1935.
21. Schulz, W.: *Ztschr. f. klin. Med.* 135: 137, 1938.
22. Shipley, R. A., and Hallaran, W. R.: *AM. HEART J.* 11: 325, 1936.
23. Skúlason, Th., and Larsen, Kaj: *AM. HEART J.* 22: 645, 1941.
24. Sprague, H. B., and White, P. D.: *J. Clin. Investigation* 1: 389, 1925.
25. Warnecke, B.: *Ztschr. f. Kreislaufforsch.* 31: 391, 1939.

THE NORMAL ELECTROCARDIOGRAM

II. ANALYSIS OF PRECORDIAL DERIVATIONS *d* AND *s* FROM 100 NORMAL PERSONS WHOSE AGES RANGED FROM 30 TO 50 YEARS

TH. SKÚLASON, M.D., REYKJAVÍK, AND KAJ LARSEN, M.D., COPENHAGEN

IN RECENT years, derivations from the precordium have been employed extensively in clinical electrocardiography. Hence an analysis of these derivations in normal persons is highly desirable. This is a big task, however, for many different precordial derivations have been in use in various clinics. But we believe that it would not be rational to prefer certain derivations from theoretical considerations alone, and, inasmuch as there is not yet sufficient clinical experience to make a choice, it will be necessary for the time being to work on a broad front.

Most of the studies reported so far on precordial derivations in normal persons deal with Lead IV, as used first by Wolferth and Wood.²⁹ This is a ventrodorsal derivation, with the exploring electrode placed either at the left sternal margin (Wolferth and Wood,²⁹ Katz and Kissin,¹⁰ Goldbloom,³ Master,¹⁷ Holzmänn⁸), or over the apex (Hoffman and Delong,⁷ Lieberman and Liberson¹⁶), and with the indifferent electrode placed on the back. Other investigators have used the now prevailing precordial derivations in which the indifferent electrode is applied either to the left leg (Wood, Bellet, McMillan, and Wolferth,³⁰ Shipley and Hallaran,²³ Robinson, Contratto, and Levine²¹), or to the right arm (Groedel,⁴ Roth,²² Wood and Selzer,³² Hoskin and Jonescu⁹) or, as suggested by Wilson, Johnston, Macleod, and Barker,²⁷ is paired with a central terminal connected through equal resistances of 5,000 or more ohms to electrodes on the right arm, left arm, and left leg (Kossmann and Johnston¹²). Finally, some investigators have reported comparative studies with several of these leads (Shipley and Hallaran,²³ Holzmänn,⁸ Sorsky and Wood,²⁴ Groedel⁵). In the following, details from these studies will be mentioned occasionally.

In this paper an analysis will be made of two precordial derivations, called *d* and *s*, from 100 normal persons whose ages ranged from 30 to 50 years. In Lead *d* the exploring electrode is placed so that its center is at the apex of the angle between the left costal margin and the xiphoid process; in Lead *s*, the exploring electrode is placed so that its center is 4 cm. to the left of, and at the level of, the apex beat. In both derivations the indifferent electrode is applied to the right arm. Our Lead *d*

From the Medical Department B, the Rigshospital, Copenhagen.
Received for publication Feb. 10, 1941.

is identical with the Lead *d* used by Groedel,⁴ whereas our Lead *s* differs from that of Groedel, for Groedel always takes his derivation from the left anterior axillary line at the level of the xiphoid process, regardless of the location of the apex beat. The reasons why we have chosen these derivations have been given in previous papers (Larsen,¹³ Larsen and Warburg¹⁵); at the conclusion of the present paper we shall repeat and elaborate our arguments. Here it will suffice merely to point out how our Leads *d* and *s* are related to the precordial derivations recommended by the American Heart Association.^{25, 26}

If only one precordial derivation is wanted, the American Heart Association recommends that it be taken from "the extreme outer border of the apex beat." With the indifferent electrode applied to the right arm, this lead, designated as Lead IVR, differs from Lead *s* in this respect, namely, that the site of derivation from the chest is located 3 to 4 cm. medial to that of Lead *s*. For taking several precordial electrocardiograms, six different sites of derivation on the chest are recommended, using one of the aforementioned indifferent electrodes, as the examiner may wish. One of the derivations obtained in this way is called Lead CR₂, and it differs from Lead *d* merely in this respect, namely, that its site of derivation on the chest is located 3 to 6 cm. more cephalad than that of Lead *d*; for CR₂ is a derivation from the left sternal margin in the fourth intercostal space, and the right arm. Another of the recommended derivations, CR₅, is identical with Groedel's Lead *s*, but differs from our Lead *s* in this, that the site of derivation does not vary with the location of the apex beat.

EXPERIMENTAL SUBJECTS AND TECHNIQUE

The present studies were carried out on 100 normal subjects whose ages ranged from 30 to 50 years; there were twenty-five women and twenty-five men aged from 30 to 40, and twenty-five women and twenty-five men aged from 40 to 50. In a previous paper (Larsen and Skúlason¹⁴) we analyzed the extremity derivations from these subjects, and gave an account of the subjects and a detailed description of the electrocardiographic apparatus and the technique employed in measuring the records.

Leads *d* and *s* were recorded simultaneously; the left arm wire was connected to the *d* electrode, and the left leg wire to the *s* electrode; the right arm electrode served as the indifferent one. The sites of derivation were determined by palpation. In cases in which the apex beat was not palpable, and when the location of the left border of the heart could not be ascertained by percussion, the *s* electrode was placed in the fifth intercostal space, with its center 4 cm. lateral to the midclavicular line. The electrodes were flat discs of rustproof steel, with a diameter of 3 cm.; two holes were punched in the electrodes, through which an elastic band kept them fixed to the chest. Pieces of felt, of the same size as the electrodes, were moistened with warm salt solution and placed under the electrodes.

As in the analysis of the extremity derivations, the present results are analyzed separately for each of the four groups of subjects, but an account is given first of the entire group, and then the records are examined with a view to sex and age

differences. For the sake of comparison with the limb leads, some of the results obtained with Lead II are included in the tabulation of the present observations.

RESULTS

The P Wave.—In ninety-nine of the 100 subjects the P wave was positive in Lead *d* and Lead *s*. In one subject the P wave was diphasic in both leads, measuring, respectively, +1.6, -0.8 mm. and +1.6, -0.6 mm. This was not the subject who showed a diphasic P wave in Lead II. Most often the P wave had the form of a rounded arch; pointed forms were infrequent. Minor notching was very common (Table I), whereas a bifid P wave occurred only twice in Lead *d* and once in Lead *s*. The average height of the P wave was 1.5 mm. in both derivations. The smallest P wave was a little less than 1 mm. in height, and the largest was hardly 2.5 mm. in height. In both derivations the average duration of the P wave was 0.10 sec. In eight subjects the duration of the P wave in one or both precordial leads was 0.12 sec. or more, and in 2 subjects it was 0.13 sec. or more.

TABLE I
THE P WAVE

	LEAD		
	<i>d</i>	<i>s</i>	II
<i>Form</i> (no. of subjects)			
Positive	99	99	99
Diphasic	1	1	1
Negative	0	0	0
Smooth	7	6	10
Notches	93	94	90
Bifid	2	1	5
<i>Size</i> (mm.)			
Minimum	0.8	0.8	0.6
Maximum	2.3	2.3	2.1
Av.	1.5	1.5	1.3
<i>Duration</i> (sec.)			
Minimum	0.078	0.078	0.083
Maximum	0.130	0.133	0.132
Av.	0.102	0.104	0.103
0.10 sec. or more (no. of subjects)	55	66	69
0.12 sec. or more (no. of subjects)	5	5	6

As is evident from Table I, the resemblance between the P wave in Leads *d* and *s* and that in Lead II (and Lead I) is so great that the same criteria for normality of the P wave may be applied to all four leads. These criteria are as follows: The P wave is positive, or, exceptionally, diphasic, with a small negative phase; its size varies from 0.5 to 2.4 mm., and its duration from 0.07 to 0.135 sec. In order to be "high," therefore, the P wave has to measure at least 2.5 mm.; and a "wide" P wave has to have a duration of at least 0.14 sec.

THE P-Q SEGMENT AND THE P-Q INTERVAL

The course of the P-Q segment was most often horizontal; less frequently it rose or fell (Table II). In eighty-one subjects the P-Q level

in Lead *d* was below the isoelectric line for a longer or shorter distance, with a maximal depression of 0.7 mm. In Lead *s* fifty-two subjects had a maximal P-Q segment depression of 0.8 mm. In one subject the P-Q segment was 0.1 mm. above the isoelectric line in Lead *d*; in another subject the same thing occurred in Lead *s*. In the rest of the records the P-Q segment kept at the level of the isoelectric line.

TABLE II
THE P-Q SEGMENT AND THE P-Q INTERVAL

	LEAD		
	<i>d</i>	<i>s</i>	II
<i>Course of P-Q segment</i> (no. of subjects)			
Horizontal	78	78	93
Rising	17	17	3
Falling	5	5	4
Isoelectric	18	47	46
Above isoelectric line	1	1	0
Below isoelectric line	81	52	54
<i>Duration of P-Q interval</i> (sec.)			
Minimum	0.120	0.119	0.121
Maximum	0.218	0.213	0.214
Av.	0.163	0.163	0.164
0.20 sec. or more (no. of subjects)	4	5	6
Less than 0.12 sec. (no. of subjects)	0	1	0

The duration of the P-Q interval was the same as in the extremity derivations (Table II). In five subjects the duration of the P-Q interval in Lead *d* and/or Lead *s* was 0.20 sec. or more. Therefore, even when the limb leads are supplemented with one or more precordial leads, the conduction time may be designated as abnormally short only if the duration of the P-Q interval in all derivations is less than 0.12 sec., whereas "prolonged conduction time" requires only that the duration of the P-Q interval be 0.22 sec. or more in at least one of the leads employed.

THE QRS COMPLEX

Form.—In Lead *d* the QRS complex was most often diphasic, consisting of an R wave and an S wave. A monophasic complex did not occur at all, whereas a triphasic complex was recorded eleven times; a Q wave was present in eleven subjects. This Q wave, which will be mentioned later, was always small; it measured only 0.3 mm. in eight subjects, and in three it measured, respectively, 0.6, 0.9 and 1.2 mm. A "second R wave," i.e., a positive wave after the S wave, was not found in any record. Table III gives additional information about the form of the QRS complex. It will be noticed that in exactly one-half of the subjects the R wave was greater than the S wave. In eighteen subjects the R wave was more than twice as large as the S wave, so that in these cases the R wave dominated the complex. Correspondingly, the S wave was the dominant wave in eleven subjects. This leaves seventy-one subjects whose R waves and S waves were about of equal size.

In Lead *s* the QRS complex was triphasic in sixty-nine subjects, consisting of a large R wave and smaller Q and S waves. A diphasic complex was found in twenty-nine subjects; it consisted of an R wave and an S wave in twenty-six, and of a Q wave and an R wave in three. A monophasic complex consisting of the R wave alone was found in two subjects. In this numerical survey the presence of a "second R wave" is left out of consideration; such a wave was present in ten subjects, and was always very small (up to 2 mm., see Fig. 1*A*). The relative size of the R wave and the S wave in the various subjects is evident from Table III. In all subjects but one the R wave was greater than the S wave, and in eighty-nine subjects the R wave was more than twice as great as the S wave, so that it was the dominating wave in the complex. In eleven subjects the R wave and the S wave were about of equal size, and in one of these the S wave was a little larger than the R wave.

TABLE III
PROPORTION OF SIZE BETWEEN THE R WAVE AND THE S WAVE

LEAD	$R > 2S$	$2S > R > S$	$2R > S > R$	$S > 2R$
<i>d</i>	18	32	39	11
<i>s</i>	89	10	1	0

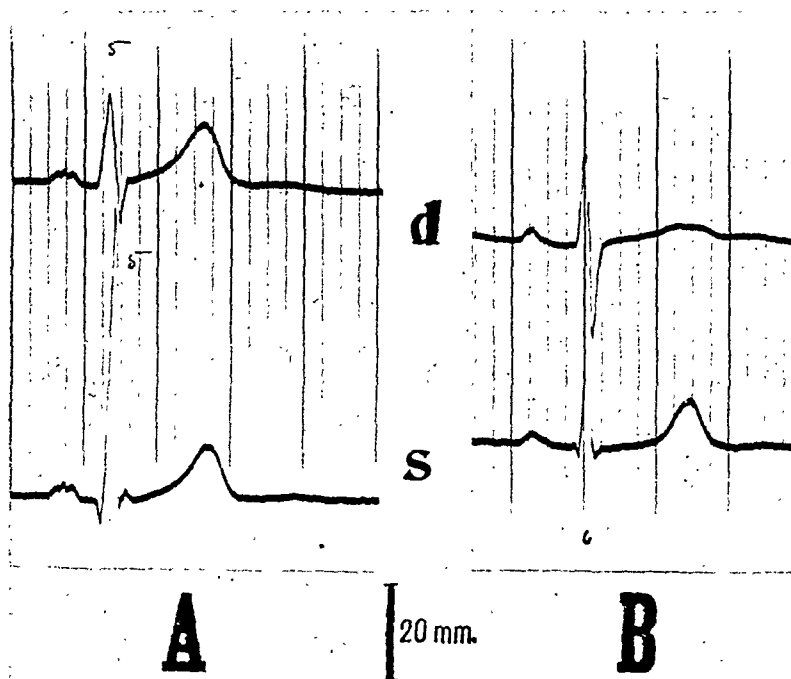


Fig. 1.—Precordial derivations *d* and *s* from two normal subjects, aged from 30 to 50 years. In *A* there is a small "second R wave" in Lead *s*; in *B* there is a plateau formation of the T wave in Lead *d*.

The occurrence of slurring and notching is recorded after the same principles as were employed by us¹⁴ previously in dealing with the extremity derivations. The result is given in Table IV. Slurring and

notching were more frequent in Lead *d* than in Lead *s*, especially of the R wave, but also of the S wave. Taking apical and basal deformities together, these phenomena were present in seventy-five subjects in the R wave in Lead *d*, and in only twenty-seven subjects in the R wave in Lead *s*; for the S wave the corresponding figures were 52 and 38. Simultaneous apical deformity of the R wave in both leads was found in thirteen subjects; in only seventeen subjects was the R wave smooth in both leads, and there was deformity of the S wave in eight of these seventeen subjects. There was no deformity of the little Q wave; although the descending limb of this wave was often thickened, it was always smooth. The notches were always small; as in the extremity derivations, the shortest limb of the notching never measured more than 1 mm. In view of the very great frequency of the nodules and notches in a series like this, we have to conclude that these deformities are of no practical significance, either in the extremity derivations or in the precordial, no matter whether they are present only in one lead or simultaneously in more, or occasionally in all the leads, and regardless of whether they are apical or basal.

TABLE IV
OCCURRENCE OF NODULES AND NOTCHING ON THE R, Q, AND S WAVES

WAVE	DEFORMITIES	LEAD			
		<i>d</i> and <i>s</i>	<i>d</i>	<i>s</i>	NONE
R	Apical	13	59	4	24
R	Apical + basal	19	56	8	17
Q	Apical + basal	0	0	0	100
S	Apical + basal	29	23	9	39

Size and Duration.—In Lead *d* the average size of the R wave was the same as that of the S wave, namely, 7.7 mm. (Table V). The smallest R wave measured 2.1 mm. in height, the highest R wave, 19.7 mm.; the S wave varied between 0.6 and 19.4 mm. The frequency and size of the Q wave in Lead *d* has been mentioned already. In Lead *s* the average size of the R wave was 23.9 mm.; the smallest R wave was 10.8 mm. in height, the highest, 45.7 mm. The S wave was present in ninety-five subjects; it varied between 0 and 22.6 mm., with an average of 5.5 mm. The Q wave was present in seventy-two subjects; it varied between 0 and 6.1 mm., with an average size of 1.2 mm. In order to get a more definite and reliable idea about the normal variations, we have calculated the dispersions (*s*) for some of the waves, as shown in Table VI, in which *m* is the average.

It is evident from the figures in Table VI that the calculated minimum limits can be of no real significance—something that is often encountered in biologic studies. In setting the limits for the normal variations (see the last column), therefore, we employed the experimental results for the minimum limits, and took the calculated values for the maximum

limits. In our series the limits established in this way were exceeded in only three subjects: in Case 83 (man, aged 37), the R wave in Lead *d* measured 19.7 mm.; in Case 45 (man, aged 40), *R_s* measured 45.7 mm.; and in Case 44 (man, aged 30), *S_s* measured 22.6 mm. The significance of small R waves will be mentioned later. The significance of large R and S waves is still unsettled.

TABLE V
THE QRS COMPLEX

	LEAD		
	<i>d</i>	<i>s</i>	II
<i>R</i> wave (size in mm.)			
Minimum	2.1	10.8	4.1
Maximum	19.7	45.7	23.4
Av.	7.7	23.9	10.2
<i>Q</i> wave (size in mm.)			
Maximum	1.2	6.1	4.4
Av.*	0.4	1.2	0.9
Present (no. of subjects)	11	72	70
<i>S</i> wave (size in mm.)			
Minimum	0.6	0.0	0.0
Maximum	19.4	22.6	5.8
Av.*	7.7	5.5	1.9
Present (no. of subjects)	100	95	79
Duration of QRS complex (sec.)			
Minimum	0.070	0.073	0.067
Maximum	0.120	0.116	0.118
Av.	0.091	0.089	0.087
0.08 sec. or more (no. of subjects)	83	78	69
0.10 sec. or more (no. of subjects)	20	11	12

*These averages are calculated per number of waves present.

TABLE VI

M (MM.)	S (MM.)	CALCULATED		MEASURED		NORMAL VARIATIONS (MM.)
		MINIMUM M-3S (MM.)	MAXIMUM M+3S (MM.)	MINIMUM (MM.)	MAXIMUM (MM.)	
<i>R_d</i> 7.7	3.1	-1.6	17.0	2.1	19.7	2 - 17
<i>S_d</i> -7.7	4.1	+4.5	-19.9	-0.6	-19.4	-0.5 - -20
<i>R_s</i> 23.9	6.5	4.6	43.3	10.8	45.7	10 - 45
<i>S_s</i> -5.5	3.7	+5.7	-16.7	0.0	-22.6	0 - -17

Several investigators (Holzmann⁸ and Wood and Selzer³²) state that in leads from the apex region the R wave is high in patients with left preponderance in the extremity leads, and, conversely, in patients with right preponderance the R wave is particularly high in the sternal derivations. Groedel⁴ has taken particular interest in the proportion between the "intrinsic deflection" in Lead *d* and the corresponding deflection in Lead *s*, and, among other things, reasoning from the studies reported by Koch and Galli,¹¹ he believes that this proportion gives reliable information about the weight proportion between the right ventricle and the left. The size of the "intrinsic deflection" may be measured by the sum of the R and T waves. In normal persons Groedel finds that the

coefficient $(R + S)_d : (R + S)_s$ varies between 1.0 and 1.5; in patients with right preponderance the coefficient is greater than 1.5, and, in patients with left preponderance, smaller than 1.0. In view of these statements we have examined both the proportion $(R + S)_d : (R + S)_s$ and the proportion $R_s : R_d$.

The value for the "intrinsic deflection" in Lead d varied between 6.7 and 31.1 mm. (averaging 15.7 mm.), and, in Lead s , between 15.6 and 62.1 mm. (averaging 29.4 mm.). The proportion $(R + S)_s : (R + S)_d$ varied between 1.08 and 3.73, averaging 2.04. Thus the "intrinsic deflection" was always greater in Lead s than in Lead d , but in no instance was it four times as large in Lead s as in Lead d . In five subjects with left preponderance in the extremity leads the average value for the above proportion was 1.78, and in eighteen subjects with a tendency toward left preponderance it was 2.07, but in these subjects there was no evidence to the effect that the preponderance of the left side was due to hypertrophy of the left ventricle. The minimum values for the sum of the R and S waves in the two derivations (6.7 mm. in Lead d and 15.6 mm. in Lead s) may be taken for guidance in deciding whether or not there is any "low voltage" in the precordial leads.

The proportion $R_s : R_d$ varied between 1.62 and 14.50, averaging 3.61. In only three subjects was the coefficient greater than 6.50, i.e., respectively, 8.40, 13.0, and 14.50, and in one of these there was a tendency toward left preponderance in the extremity derivations. In the five subjects with left preponderance in the extremity derivations the average of the above-mentioned proportion was 3.26, and in the eighteen subjects with a left preponderance tendency it was 3.77.

The average duration of the QRS complex was 0.091 sec. in Lead d , and 0.089 sec. in Lead s , i.e., a little bit longer in the precordial leads than in the limb leads. Including the derivations in which the QRS complex was of the longest duration, it is found that this was the case in five subjects in Lead I, in thirteen subjects in Lead II, in twenty-seven in Lead III, in forty-five in Lead d , and in thirty-six in Lead s (the number of subjects counted in this way exceeds 100 because the QRS complex in some cases was equally long in two or three leads and longer than in the other derivations). In several cases the duration of the QRS complex was 0.10 sec. or more. Considering all five derivations together, it was found that the duration in twenty-three subjects was between 0.10 and 0.12 sec. in at least one derivation. We take such a duration of the QRS complex as normal for the age groups here considered, except in cases in which a previous electrocardiogram had shown a shorter duration.

Other Aspects of the QRS Complex.—All investigators agree in looking upon *complete absence of the R wave* in the precordial leads as pathologic. This phenomenon was observed first by Wilson, Macleod,

Barker, Johnston, and Klostermeyer²⁸ in cases of anterior cardiac infarction, but later it was encountered with many other lesions, especially those which produce bundle branch block or marked preponderance of the left side (e.g., Holzmänn,⁸ Master, Dack, Kalter, and Jaffe¹⁸). In other patients with the same lesions the records have shown an *abnormally small R wave*, and the limit for such a wave is set by most investigators at 2 mm. None of these changes occurred in our series. According to our observations, the R wave may be designated as abnormally small if it is less than 2 mm. in Lead *d*, and less than 10 mm. in Lead *s*.

Holzmänn⁸ looks upon complete absence of the R wave in the precordial leads as a result of *abnormal increase in the S wave at the expense of the R wave*, and he states that the proportion R:S in the derivation employed by him—from the left sternal margin to the back—in normal subjects is never as small as 1:10. In Lead *d* the proportion R:S varied between 10.3 and 0.21, and this means that the S wave in Lead *d* in our 100 subjects was never five or more times greater than the R wave. In Lead *s*, as mentioned before, only one subject had an S wave which was greater than the R wave.

“M” and “W” complexes, which have been observed by Wood and Wolferth,³¹ Mortensen,¹⁹ and others, in cardiac infarction, and which are present also in cases of bundle branch block, did not occur in any of our subjects.

The presence of a *Q wave in the precordial sternal derivation* is emphasized by Mortensen^{20b} as the most frequent and most characteristic change in the QRS complex in cases of anterior cardiac infarction. In normal persons Mortensen has never seen a Q wave in the sternal derivation employed by him, namely, CF₂ (from the left sternal margin in the fourth intercostal space to the left leg). In Lead *d* we found a Q wave in eleven of our 100 normal subjects; the largest Q wave was 1.2 mm. Therefore, we have to conclude that in Lead *d* the Q wave must measure at least 2 mm. in order to be designated as abnormal. It may be added that Holzmänn⁸ states that a T wave in the derivation from the left sternal margin, at the attachment of the fifth rib, to the left leg, is not pathologic.

THE S-T SEGMENT

In a great majority of the records the S-T segment was slanting upward (Table VII), and very frequently its transition into the ascending branch of the T wave was very gradual, so that it was impossible to locate the end of the S-T segment and the beginning of the T wave. In other cases the rise of the curve was accentuated, and the accentuation presumably corresponded to the beginning of the T wave. A saddle-shaped S-T segment occurred ten times in Lead *s*—in seven of these records together with a “second R wave,” and three times in connection

with absence of the S wave. In Lead *d* the S-T segment was saddle-shaped in only one subject, in whose record there was a small, notched S wave.

TABLE VII
THE S-T SEGMENT

Course	LEAD		
	<i>d</i>	<i>s</i>	II
Horizontal (no. of subjects)	1	1	12
Rising (no. of subjects)	98	89	75
Falling (no. of subjects)	0	0	0
Saddle-shaped (no. of subjects)	1	10	13
Isoelectric (no. of subjects)	5	18	36
Above isoelectric line (no. of subjects)	87	65	44
Maximal elevation (mm.)	2.8	2.4	0.9
Below isoelectric line (no. of subjects)	8	17	20
Maximal depression (mm.)	0.2	0.8	0.5

In measurements taken 0.05 sec. after the end of the QRS complex, the level of the S-T segment was above the isoelectric line in eighty-seven subjects in Lead *d*, and in sixty-five subjects in Lead *s*; the maximal elevation was 2.8 mm. in Lead *d*, and 2.4 mm. in Lead *s*. The S-T segment was found below the isoelectric line, but sloping upward, eight times in Lead *d* and seventeen times in Lead *s*; the maximal depression occurred in Lead *s*, and amounted to 0.8 mm. Therefore, when the level of the S-T segment is 1 mm. or more below the isoelectric line, it may be designated as abnormal, and, likewise, if the level of the S-T segment is 3 mm. or more above the isoelectric line. But, as in the extremity derivations, it is doubtful whether an abnormally high level of the S-T segment is of any pathologic significance in cases in which the form of the S-T segment is normal.

If in the precordial leads we establish the isoelectric line as a horizontal line through the P-Q segment, we have to require that the S-T level fall 1 mm. or more below this line in order to be able to characterize the course of the S-T segment as abnormally negative. Since the P-Q segment in Leads *d* and *s* often falls below the isoelectric line proper, we will thus be unable to make the diagnosis of "abnormally negative S-T segment" in several of those cases in which the S-T level is from 1 to 1.8 mm. below the true isoelectric line, and in which the P-Q level at the same time is negative (cf. the preceding paper on the extremity derivations¹⁴).

THE T WAVE

In both Lead *d* and Lead *s*, the T wave was positive in all of the 100 subjects, and took the form of a gradual, smooth curve; the higher this wave, the more pointed was its form. An exception to this rule occurred in two cases in Lead *d*, in which the highest part of the curve formed a plateau (the precordial derivation from one of these subjects is shown

in Fig. 1B). (In a few normal persons, who are not included in this series, we have seen a little depression in the middle of the plateau here described, so that the T wave in these cases had a two-humped appearance.)

TABLE VIII
THE T WAVE

	LEAD		
	<i>d</i>	<i>s</i>	II
<i>Form</i>			
Positive (no. of subjects)	100	100	100
<i>Size (mm.)</i>			
Minimum	0.9	1.3	1.1
Maximum	10.6	19.2	5.8
Av.	4.5	7.1	3.0
10 mm. or more (no. of subjects)	1	14	
Less than 1 mm. (no. of subjects)	2	0	

In Lead *d* the average size of the T wave was 4.5 mm.; in Lead *s* it was 7.1 mm. In two subjects the T wave in Lead *d* measured only 0.9 mm. The smallest T wave in Lead *s* was 1.3 mm. Hence a T wave smaller than 1 mm. will always be suspect; and diphasic and negative T waves (in these age classes) are always abnormal. The dispersion for the T wave in Lead *d* was 2.3 mm.; in Lead *s* it was 3.0 mm. Therefore, the limit for the normal height of the T wave in Lead *d* may be set at 12 mm., and in Lead *s* at 17 mm. In our series these limits were exceeded only once, namely, in Case 25 (man, aged 41) in which the T wave in Lead *s* measured 19.2 mm. in height; the next in height, in Lead *s*, measured 13.4 and 13.0 mm. Most other investigators (e.g., Katz and Kissin,¹⁰ Wood and Wolferth,³¹ and Holzmänn⁸) set the limit for the normal height of the T wave at 9 or 10 mm. In fourteen of our subjects the T wave in Lead *s* measured more than 10 mm., and in one of these the T wave was higher than 10 mm. in Lead *d*, also.

THE Q-T INTERVAL

For the normal duration of the Q-T interval in Lead II, Larsen and Skúlason¹⁴ have derived the following formula: $Q-T = \frac{1}{8} R-R + 0.28 \pm 0.05$ sec., in which Q-T and R-R stand for the average duration of the Q-T and R-R intervals in seconds. Analysis shows that this formula is applicable also to Lead *d* and Lead *s*.

SEX AND AGE DIFFERENCES

The investigation of this question was carried out for these derivations in the same manner as for the limb leads.¹⁴ As is evident from Table IX, the average height of the QRS complex and of the T wave was found to be greater in the men than in the women; likewise, the average duration of the P wave, P-Q interval, and QRS complex was greater in the

men than in the women. Some of the waves showed a statistically significant age difference (indicated by italic figures in Table IX). A statistically significant difference was found also in the S-T level in Lead *s*; this segment was above the isoelectric line more often in men than in women. There was no particular difference between the two age classes.

TABLE IX
SEX AND AGE DIFFERENCES

	MEN	WOMEN	30-40 YEARS	40-50 YEARS
<i>Av. height of waves (mm.)</i>				
R wave in Lead <i>d</i>	8.4	6.9	7.6	7.7
S wave in Lead <i>d</i>	9.0	6.9	8.2	7.6
"The intrinsic deflection" in Lead <i>d</i>	17.5	13.7	15.7	15.3
T wave in Lead <i>d</i>	6.0	3.0	4.4	4.5
R wave in Lead <i>s</i>	26.7	22.1	23.2	24.7
S wave in Lead <i>s</i>	6.6	4.5	6.4	4.7
"The intrinsic deflection" in Lead <i>s</i>	33.3	26.6	29.5	29.4
T wave in Lead <i>s</i>	8.4	5.8	7.2	7.0
<i>Av. duration (sec.) (Lead d)</i>				
P wave	0.105	0.101	0.100	0.105
P-Q interval	0.169	0.158	0.162	0.164
QRS complex	0.094	0.086	0.091	0.090
<i>Other components (no. of subjects)</i>				
S-T positive in Lead <i>s</i>	42	23	37	28
"Second R wave" in Lead <i>s</i>	6	4	5	5
Saddle-shaped S-T in Lead <i>s</i>	5	5	3	7

CORRELATIONS

The correlation between the components of the precordial derivations was studied by means of graphic methods, and, in doubtful cases, by calculation of the correlation coefficient (*r*).

TABLE X

R-R interval and (R + S) _d	$r = + 0.04 \pm 0.100$
R-R interval and (R + S) _s	$r = + 0.15 \pm 0.098$
R-R interval and T _d	$r = + 0.59 \pm 0.064$
R-R interval and T _s	$r = + 0.50 \pm 0.075$

The correlations given in Table X were found between the duration of the R-R interval and the size of the "intrinsic deflection" (R + S), and between R-R and the T wave in Leads *d* and *s*.

It will be noticed that a high T wave was more frequent in persons who at rest have a slow pulse rate than in those who at rest have a faster pulse rate. On the other hand, there was no correlation between the size of the intrinsic deflection and the duration of the R-R interval. This confirms our observations on the extremity derivations, namely, that those components of the electrocardiogram which are caused by the contraction of the myocardium are dependent upon the pulse rate to a greater extent than those caused by propagation of the impulse.

Between the size of the components of the QRS complex and the height of the T wave, correlations were found as shown in Table XI.

TABLE XI

R_d and T_d	$r = + 0.15 \pm 0.098$
$(R + S)_d$ and T_d	$r = + 0.40 \pm 0.084$
R_s and T_s	$r = + 0.36 \pm 0.087$
$(R + S)_s$ and T_s	$r = + 0.46 \pm 0.079$
$(R + S)_d$ and $(R + S)_s$	$r = + 0.60 \pm 0.064$
T_d and T_s	$r = + 0.70 \pm 0.051$

Thus, in Leads d and s there was a positive correlation between large intrinsic deflections and large T waves. On the other hand, in contrast to Lead s , Lead d showed no correlation between large R waves and large T waves because the S wave in Lead d , in contrast to Lead s , makes up an essential part of the intrinsic deflection. These studies show that a large QRS complex in the various derivations is associated more often with a large T wave in the same derivations than with a low T wave. The two last coefficients show further that the occurrence of a large QRS complex and a high T wave in one precordial derivation most often will be associated with large waves in the other precordial derivation. That large waves in the precordial derivations most often are associated with large waves in the extremity derivations (at any rate in one of these leads) is evident from the analyses in Table XII.

TABLE XII

Greatest $(R + S)$ in Leads I, II, or III and $(R + S)_s$	$r = + 0.34 \pm 0.088$
Highest T wave in Leads I, II, or III and T_s	$r = + 0.073 \pm 0.047$

We have further sought to find out whether there was any correlation between the size of the waves and the size of the experimental subject, as measured by the body surface, but there was no such correlation (Table XIII). Nor was there any correlation between the size of the waves and excessive weight or less than average weight of the experimental subjects, i.e., their weight in percentage of the normal weight.

TABLE XIII

Body surface and $(R + S)_s$	$r = + 0.16 \pm 0.097$
Body surface and T_s	No correlation (diagram)

DISCUSSION

Shortly before the appearance of the proposal made by the American Heart Association^{25, 26} about standardization of precordial leads, Larsen and Warburg¹⁵ had presented the following principle, which they considered the most rational for the connection of the leads in taking a precordial electrocardiogram: *The connection of the leads, the polarity of the galvanometer, and the direction of travel of the photographic*

recording medium should agree mutually in such a way that, when a negative potential is impressed on the exploring electrode, it would be recorded as a downward deflection; the curve would be read from the start (at left) towards the right. This principle is founded partly on the fact that it is in keeping with the general principles for graphic recording, and partly on the fact that the nomenclature proposed by Einthoven for derivations from the extremities is, in this way, readily applicable to the precordial leads, also. Both the precordial leads recommended by the American Heart Association and the Leads *d* and *s* which were employed in the present studies are in harmony with the above principle. The most important practical result of this is that persons who have positive P and T waves in Leads I and II usually will have positive P and T waves in the precordial leads, so that one avoids the "mirror-reflected" electrocardiograms which were obtained with the "older" connection of the leads (cf., for instance, Wolferth and Wood²⁹).

The American Heart Association did not wish to make any final decision as to the location of the indifferent electrode. Most examiners now apply the electrode to either the left leg or the right arm. As is evident from the studies reported by Shipley and Hallaran,²³ Sorsky and Wood,²⁴ and Edwards and Vander Veer,¹ pairing the precordial electrode with one on the left leg in normal, adult subjects gives either positive, diphasic, or negative P waves, and, also, but only in the sternal *d*-like derivations, either positive, diphasic, or negative T waves. The significance of the T wave in such derivations is therefore reduced greatly, i.e., it is limited chiefly to those changes that appear during the observation of the patient. In contrast thereto, a diphasic or negative T wave (and P wave) in a derivation from the precordium to the right arm is always abnormal (in adults). In our opinion, this difference shows conclusively that it is preferable to place the indifferent electrode on the right arm, rather than on the left leg.

As to the location of the exploring electrode, it is to be mentioned that an increasing number of examiners prefer and recommend the employment of at least two precordial leads, namely, one from the left side of the heart and one from the right side (Groedel,⁴ Roth,²² Holzmänn,⁸ Freundlich and Lepeschkin,² Mortensen,^{20a} Robinson, Contratto, and Levine,²¹ and Wood and Selzer³²). We have selected Lead *d* and Lead *s* because Groedel's investigations suggest that Lead *d*, particularly, will give information about the condition of the right ventricle, and Lead *s*, particularly, about the condition of the left ventricle. Groedel and Koch⁶ have shown that a potential maximum for the intrinsic deflection corresponding to the right ventricle is found at the xiphoid process, and that the corresponding potential maximum for the left ventricle is located a few centimeters lateral to the apex of the heart. Therefore, the sites of derivation from the precordium should

vary according to the position of the heart. This applies in particular to Lead *s*; it may be justifiable to let the site of derivation for Lead *d* be determined by the external topographic landmarks, for the location of the right ventricle is far less variable than that of the left ventricle under pathologic conditions. Whether there is any reason to prefer Leads *d* and *s* to the leads recommended by the American Heart Association—Leads CR₂ and IVR (see the introduction)—is a question we cannot yet decide; at present, members of our department are collecting material to elucidate this question. Still, it may be mentioned now that Lead *s* offers one advantage over Lead IVR, for Larsen¹³ and Roth²² have shown that derivations in which the exploring electrode is located a little outside the apex of the heart are easier to reproduce than derivations in which the exploring electrode is placed just over the apex of the heart.

SUMMARY

The present work is an analysis of precordial derivations *d* and *s* from 100 normal subjects (fifty women and fifty men), whose ages ranged from 30 to 50 years. In Lead *d* the exploring electrode is placed so that its center is located at the apex of the angle between the left costal margin and the xiphoid process. In Lead *s* the exploring electrode is placed so that its center is located 4 cm. to the left of the apex of the heart, and at the level of the apex. In both of these leads the electrode on the right arm serves as the indifferent one. "Modern" connection of the leads is employed. The more important results are evident from the tables.

REFERENCES

1. Edwards, J. C., and Vander Veer, J. B.: *AM. HEART J.* 16: 431, 1938.
2. Freundlich, J., and Lepeschkin, E.: *Cardiologia* 3: 331, 1939.
3. Goldbloom, A. A.: *Am. J. M. Sc.* 187: 489, 1934.
4. Groedel, F. M.: *Das Extremitäten-, Thorax- und Partialelektrokardiogramm des Menschen*, Dresden and Leipzig, 1934, Theodor Steinkopff.
5. Groedel, F. M.: *Cardiologia* 3: 23, 1939.
6. Groedel, F. M., and Koch, E.: *Ztschr. f. Kreislaufforsch.* 26: 18, 1934.
7. Hoffman, A. M., and Delong, E.: *Arch. Int. Med.* 51: 947, 1933 (I).
8. Holzmänn, M.: *Arch. f. Kreislaufforsch.* 1: 2, 1937.
9. Hoskin, J., and Jonescu, P.: *Brit. Heart J.* 2: 33, 1940.
10. Katz, L. N., and Kissin, M.: *AM. HEART J.* 8: 595, 1933.
11. Koch, E., and Galli, W.: *Ztschr. f. Kreislaufforsch.* 26: 204, 1934.
12. Kossmann, C. E., and Johnston, F. D.: *AM. HEART J.* 10: 925, 1935.
13. Larsen, Kaj: *Hospitalstidende* 79: 785, 1936; *AM. HEART J.* 14: 1, 1937.
14. Larsen, Kaj, and Skúlason, Th.: *AM. HEART J.* 22: 625, 1941.
15. Larsen, Kaj, and Warburg, E.: *Hospitalstidende* 80: 276, 1937; *AM. HEART J.* 14: 7, 1937.
16. Lieberman, A., and Liberson, F.: *Ann. Int. Med.* 6: 1315, 1933.
17. Master, A. M.: *AM. HEART J.* 9: 511, 1934.
18. Master, A. M., Dack, S., Kalter, H. H., and Jaffe, H. L.: *AM. HEART J.* 14: 297, 1937.
19. Mortensen, Vagn: *Hospitalstidende* 79: 1233, 1936; *Acta med. Scandinav.* 92: 603, 1937.
20. Mortensen, Vagn: *Nordisk Medicin*, 1939, Vol. II, (a) p. 1971, (b) p. 2749.
21. Robinson, R. W., Contratto, A. W., and Levine, S. A.: *Arch. Int. Med.* 63: 711, 1939.

22. Roth, J. R.: AM. HEART J. 10: 798, 1935.
23. Shipley, R. A., and Hallaran, W. R.: AM. HEART J. 11: 325, 1936.
24. Sorsky, E., and Wood, P.: AM. HEART J. 13: 183, 1937.
25. Standardization of Precordial Leads, AM. HEART J. 15: 107, 1938.
26. Standardization of Precordial Leads: Supplementary Report, AM. HEART J. 15: 235, 1938.
27. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: AM. HEART J. 9: 447, 1934.
28. Wilson, F. N., Macleod, A. G., Barker, P. S., Johnston, F. D., and Klostermeyer, L. L.: HEART 16: 155, 1933.
29. Wolferth, C. C., and Wood, F. C.: Am. J. M. Sc. 183: 30, 1932.
30. Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C.: Arch. Int. Med. 52: 752, 1933 (II).
31. Wood, F. C., and Wolferth, C. C.: AM. HEART J. 9: 706, 1934.
32. Wood, P., and Selzer, A.: Brit. Heart J. 1: 49, 1939.

THE SIGNIFICANCE OF THE TENSILITY OF THE AORTA AS AN INDEX OF THE AGING PROCESS IN THE ANIMAL BODY

JEAN HUME NELBACH, B.A., M.P.H., AND L. P. HERRINGTON, A.M., PH.D.
NEW HAVEN, CONN.

IN AN earlier communication, one of the authors (Hume¹) reported a new procedure for measuring the tensility of the aorta of the rat. Evidence was presented indicating the value of this test as a measure of the normal aging process in the animal organism and of various environmental factors influencing that process.

In these experiments the Hume tensometer apparatus, which applies a gradually increasing stress to a 1 cm. ring of the aorta, was used to record the association between force applied and amount of stretch. From these observations Young's modulus of elasticity could be computed for each degree of stress, and a curve constructed relating the change in the value of the modulus to change in stress. Since the experiments proceeded from zero tension to the breaking point with each aorta ring, no measurement of elasticity (in the sense of an ability to regain an original length after stretching) was involved. The results were expressed in terms of the modulus, principally because rates of change in stretch and stress gave a clearer picture of tensile behavior than absolute values.

In general, all aortas gave a characteristic curve when the moduli for successive points were plotted against the successive stresses at these points, as observed during progressive stress. The tensile resistance at first decreased to a minimum point (loads from zero to 54 Gm.). This decrease is probably related to the normal elasticity of the wall. Further increase in stress led to a progressive increase in tensile resistance in a practically linear manner, until the point of rupture. Although there were interesting differences in the initial limb of the curve and in the points of inflection in different experimental groups, the groups were most strikingly distinguished by the slope of the long ascending limb, and, in some instances, by the ultimate tensile strength (weight supported at point of rupture).

The earlier data for individual groups indicated that both increasing age and higher environmental temperatures decreased the ability of the

Contribution No. 33 from the John B. Pierce Laboratory of Hygiene.
Received for publication March 5, 1941.

aorta to resist distention stresses. Both alcohol and lead intoxication increased tensile resistance slightly above the values obtained for the control group, a result which, in the alcohol group, was associated with retarded growth.

The authors are well aware that the above conclusions were based upon a technique which does not duplicate the stress conditions of normal function, either in regard to the mode in which force is applied or the absolute values for the force. In this sense the method is distinct from that employed in investigations in which hydrostatic pressure has been applied to distend arterial sections,² or in which the factor of elasticity has been studied with forces largely within the range of physiologic values.³ A physically determined index of tensility yields, however, a very precise picture, and the results discussed above strongly suggest that the structural factor which was measured is responsive to several important environmental variables. For this reason the present experiments were planned to check the above conclusions on age and temperature, and have been extended to two new variables, namely, (1) the effect of a continuing environmental disturbance of the nervous system and (2) the ingestion of thyroid extract.

APPARATUS AND TECHNIQUE

No change was made in the tensometer, which was fully described in a previous publication.¹ Groups of forty animals were exposed to temperatures of 65° F., 83° F., and 95° F. in group cages provided with temperature regulation. When temperature was not an experimental variable, the cage temperature was held at 83° F. The animals were male albino rats from a common source, and their experimental exposures were begun when they were 60 days old. Fifty per cent of each group were sacrificed at the age of 120 days and 210 days, respectively. Since the groups were started serially at approximately weekly intervals, it was possible to equate the mean initial weights within narrow limits. Animals were weighed at weekly intervals, and mean growth curves were computed. In all cases a standard ration was fed, except in the case of the "thyroid" group, in which this ration was supplemented with 0.6 Gm. of desiccated thyroid (Lilly, U.S.P. Thyroid) per 1,000 Gm. of basic ration. One gram of this desiccated thyroid preparation is equivalent to 5 Gm. of fresh thyroid. The proportion of thyroid to food was 0.06 per cent by weight.

In order to obtain a disturbing feature in the temperature-controlled cage of the "disturbed" group, a telechron-controlled switching box was constructed which produced at set intervals a series of exciting stimuli. These were three in number, and included a ringing bell, vibration and noise, and a sudden blast of air. During each hour a sixteen-minute period of disturbance was produced. This consisted at first of a bell ringing (ten minutes), vibration and noise (five minutes), and a blast of air at high velocity (one minute). The order and length of time of these stimuli were varied from time to time in order to prevent conditioning to any one combination of disturbances. The bell was an ordinary door bell; the blower was of the centrifugal type, and delivered about 150 cubic feet per minute. Vibration and noise were produced by mounting an $\frac{1}{8}$ horsepower electric motor, provided with an

eccentric shaft, on a galvanized sheet at one end of the inner cage. Rotation of this shaft at the rate of about 120 revolutions a minute produced a thumping noise and a violent "shimmy" in the cage.

PLAN OF EXPERIMENTS

1939

Five groups of male albino rats, aged 60 days at the beginning of the experiments, were used. Each group consisted of forty-five animals; twenty were sacrificed at 120 days and twenty at 210 days, allowing a margin of five to take care of any mortalities suffered by the group. The five groups were scheduled as shown in Table I.

TABLE I

EXPERIMENT NO.	13 AND 18	12 AND 17	10 AND 15	11 AND 16	9 AND 14
Treatment	Disturbed	Thyroid*	Normal control	High temperature	Low temperature
Temperature (°F.)	83	83	83	95	65
Entered cages	4/14	4/21	4/28	5/5	5/12
Sacrificed, first 20	6/13-14	6/20-21	6/27-28	7/4-5	7/11-12
Sacrificed, second 20	9/11-12	9/18-19	9/25-26	10/2-3	10/9-10

*0.06 per cent, desiccated, in diet.

Several days of physiologic conditioning were allowed for the 65° F. and 95° F. groups, while the temperatures were gradually lowered or raised. A chart for daily temperature readings was attached to each cage, with space for a recording of the total weight of the animals in each cage at weekly intervals. Particular care was taken to see that the thyroid and 95° groups had sufficient water at all times. All groups received the standard Bal-O-Ration diet ad lib.

1940

Three groups of male albino rats, aged 60 days at the beginning of the experiments, were used. Each experiment ran for sixty days, so that at the time of sacrifice these animals were 120 days old. The schedule of experiments is given in Table II.

TABLE II

EXPERIMENT NO.	21	20	19
Treatment	Disturbed	Normal controls	Low temperature
Temperature (° F.)	83	83	65
Entered cages	3/11	3/13	3/15
Sacrificed	5/13-14	5/15-16	5/17-18

At the time of sacrifice an aorta ring from each rat was preserved for section and histologic examination, in addition to the section used for stretching. The following structures were also removed and fixed for later study: (1) heart, (2) liver, (3) testes (weighed together), (4) pituitary, (5) adrenals (weighed together), and (6) prostate and seminal vesicles (weighed together). The results of the examination of these tissues will be reported in a later paper.

RESULTS

Perhaps the most general evaluation of the tensility factor can be obtained from a comparison of curves for various treatments and ages in

relation to the mean curve for all experiments over the three years of work. Fig. 1 is a master graph which contrasts the following curves: A_1 , the mean curve for all groups, regardless of age or treatment (1939-1940); A_2 , the same as A_1 , but including also 1937 and 1938; B , for all groups exposed to low temperature, regardless of age; C , for all groups at moderate temperatures, regardless of age; D , for all groups at high temperature, regardless of age; E , for all groups at 120 days of age, regardless of treatment; and F , for all groups at 210 days of age, regardless of treatment. Although a statistical assessment must be made of the reliability of these apparent differences, some orderly relation must appear in such a graph if age and treatment have had a positive effect. The ordinate value "E" represents a modulus of elasticity, and is computed from the following formula:

$$E = \frac{F}{a} \cdot \frac{L}{dl}$$

in which

$$\begin{aligned} F &= \text{force applied,} \\ a &= \text{area cross section,} \\ L &= \text{original length,} \\ dl &= \text{change in length.} \end{aligned}$$

In earlier experiments,¹ groups exposed to a low environmental temperature gave a tensility curve which was strikingly different from that of other groups, and was in the direction of the high tensile resistance which was found to be typical of young animals. In Fig. 1, curve B , which includes three other groups raised at 65° F., we observe this effect again, indicating a higher tensile resistance for the 65° group than for any other.

Below curve A_2 , the grand average of *all* experiments, we find the mean curves for all other groups. In point of placement on the graph, we find that the addition of three groups to the original moderate-temperature experiments, and of two groups to the high-temperature experiments, results in a descending order for curves B , C , D (low, moderate, and high temperature), in which tensile resistance decreases as the temperature increases. These graphic separations have been statistically assessed by two methods; both methods were applied to the ascending limb of the curves. The first analysis consisted of testing the variance within each experiment due to individual regressions against the variance between experiments from average regression. Snedecor's F test, based on Fisher's Z test, was used as the criterion for significance of variance between trends of curves. The second analysis consisted of testing the significance of difference between mean E 's by the same test.

In Fig. 1 a gross age comparison is also presented. Curves E and F are, respectively, the mean curves for all animals 120 and 210 days old,

regardless of temperature exposure or other treatment. Although the separation is less striking we find again that the addition of eight groups 120 days* old and five groups 210 days old to the earlier data has sustained the original conclusion that increasing age is associated with decreasing tensile resistance in aortic rings. The comparison between 120-day and 210-day groups of any one year reveals separate and distinct curves, with a slight overlapping of the most easily stretched young aortas and the least easily stretched older aortas. Statistical tests of differences between the means of the 120-day and 210-day groups proved significant or highly significant except for the "disturbed" groups. Likewise, the differences between the regressions of these same groups showed significant differences except for the "thyroid" and "disturbed" groups. The 95° F. groups were on the border line.

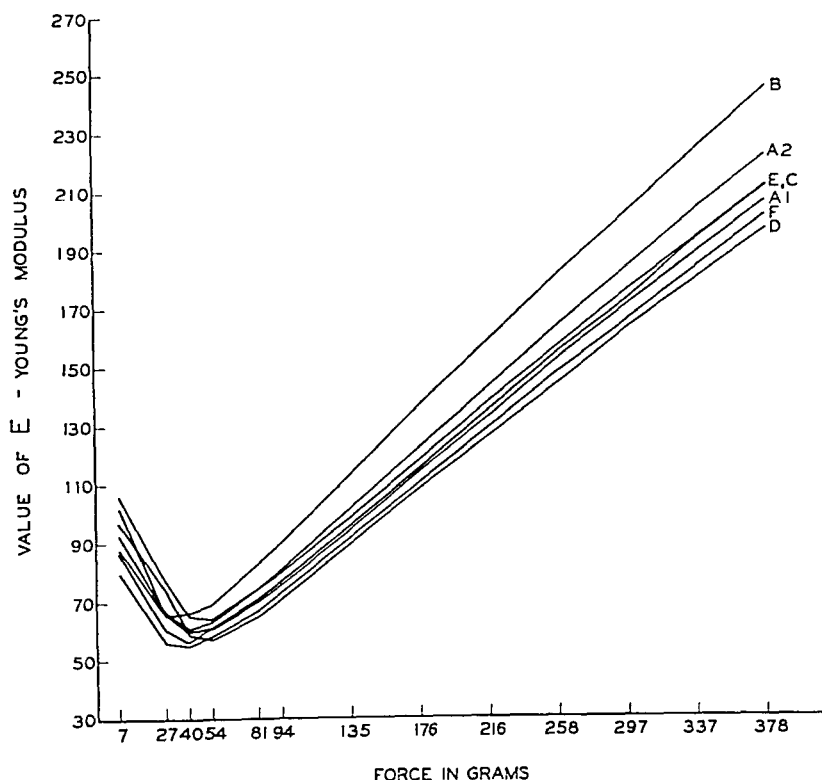


Fig. 1.—Graph of average curves *B*, for all observations at low temperature, irrespective of age; *A*₂, for all observations made, including the 1937-1938 data; *E*, for all observations made on animals 120 days of age, regardless of treatment; *C*, for all observations made at medium temperature, regardless of age; *A*₁, for all observations made during 1939 and 1940; *F*, for all observations made on animals 210 days old, regardless of treatment; and *D*, for all observations at high temperature, irrespective of age.

The question now arises as to the extent to which these general statistical conclusions can be supported by the curves for temperature at a given age and for age at a given temperature. In Fig. 2 the mean tensility curves for all groups at the standard age of 120 days have been

*There were no 120-day groups in the earlier data.

plotted. Curves for the "disturbed" and thyroid-fed groups have been included for this age, but the immediate comparison of importance involves the three temperature curves. Even casual inspection of these tensility curves shows that the general conclusion as to the temperature effect on tensility is further supported by data obtained when age is experimentally constant at 120 days. Statistical tests of this graphic separation show that there is a highly significant difference between the regressions of each group except the 95° F. and the "thyroid" groups of 1939.

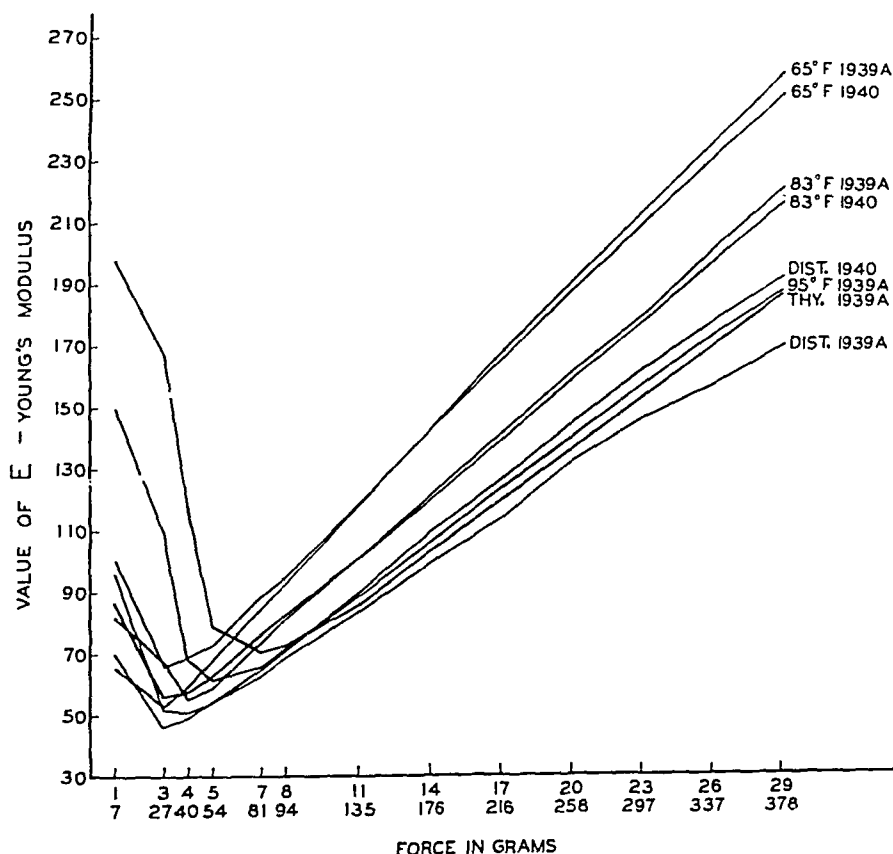


Fig. 2.—Graph of 120-day observations, showing the effects of different treatments at one given age.

In comparing the means of these eight 120-day groups, a highly significant difference was found between the temperature groups. However, no significant difference was found between the 95° F. and "thyroid," the 95° F. and "disturbed," and the "thyroid" and "disturbed" groups of 1939. To strengthen the evidence, there was no significant difference between the 65° F. experiments done in 1939 and 1940, the 83° F. experiments of 1939 and 1940, and the "disturbed" experiments of the two years.

In Fig. 3 a similar comparison of temperature effects has been made for the standard age of 210 days. The inverse correlation of tensile resistance with environmental temperature is not perfect for the data as a whole at the age of 210 days. Analysis of the results by years

shows that in the original experiments the clearest association of temperature was with high tensile resistance in the low temperature group, and with lower tensile resistance in the moderate and high groups. The means of the two latter were not significantly different. In the experiments done in 1939, the order confirms perfectly the effect noted at the age of 120 days. It should be pointed out, however, that a 5° higher temperature was used in the hot cages and also that the 1939 curves are all placed somewhat lower than those for 1937-1938. The true explanation of this latter effect is not known. It may have been the result of obtaining animals from a different source, which seemed advisable because a number of animals received from the first source at the beginning of one unfinished series were thought to be infected with middle ear disease. These were destroyed and a new source used. In any event, we find that a combination of the two curves for low, medium, and high temperatures, respectively, in this series, gives a clear separation between the low temperature and the medium and high, with only a small difference between medium and high groups. This was noted in the original study.¹

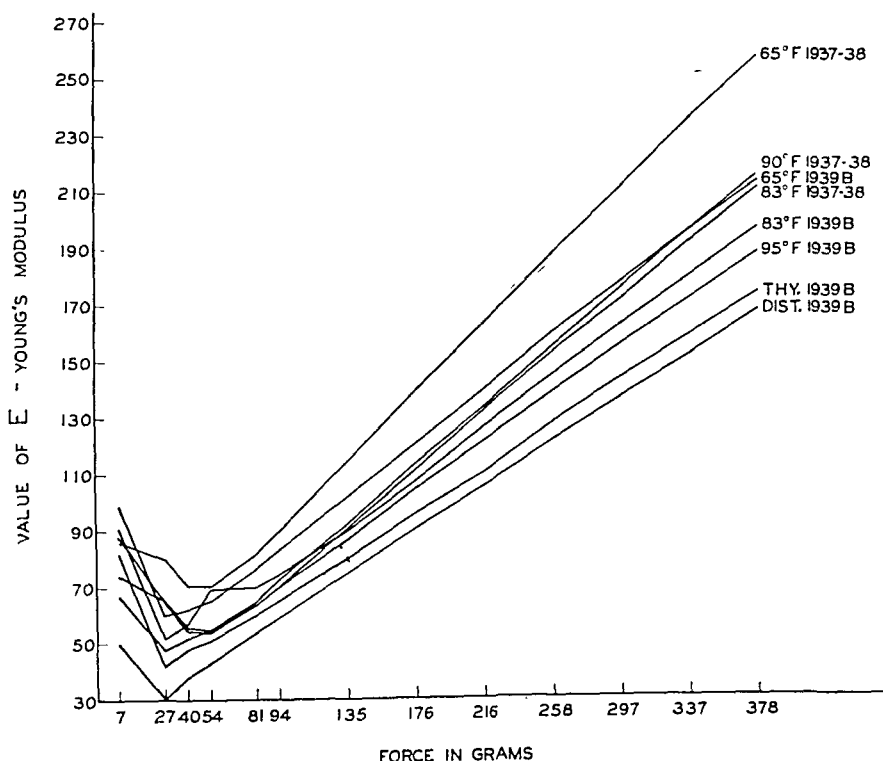


Fig. 3.—Graph of the 210-day observations, showing the effects of different treatments at a given age of 210 days.

In similar manner, a more refined estimate of the effects of age, independent of temperature, may be gained through a study of Fig. 4. Here the curves for the three temperature groups have been plotted, and

the age noted opposite the individual temperature curves. A separation between years in which the experiments were performed is apparent here, as well as in the temperature effects at the age of 210 days. The principal conclusion, however, that for a standard temperature tensile resistance decreases with increasing age, is still borne out. For four groups at 65° F., four at 83° F., and two at 95° F., we find within each separate temperature group a lower mean tensile resistance for the older groups (marked B). The trend of all experiments, regardless of series, justifies this conclusion. Statistically, however, it is probably most sensible to test the age hypothesis within a single year's series. For example, we find that in the 65° F. group in 1939, the 120- and 210-day subgroups differ significantly from each other, both as to regression and as to mean.

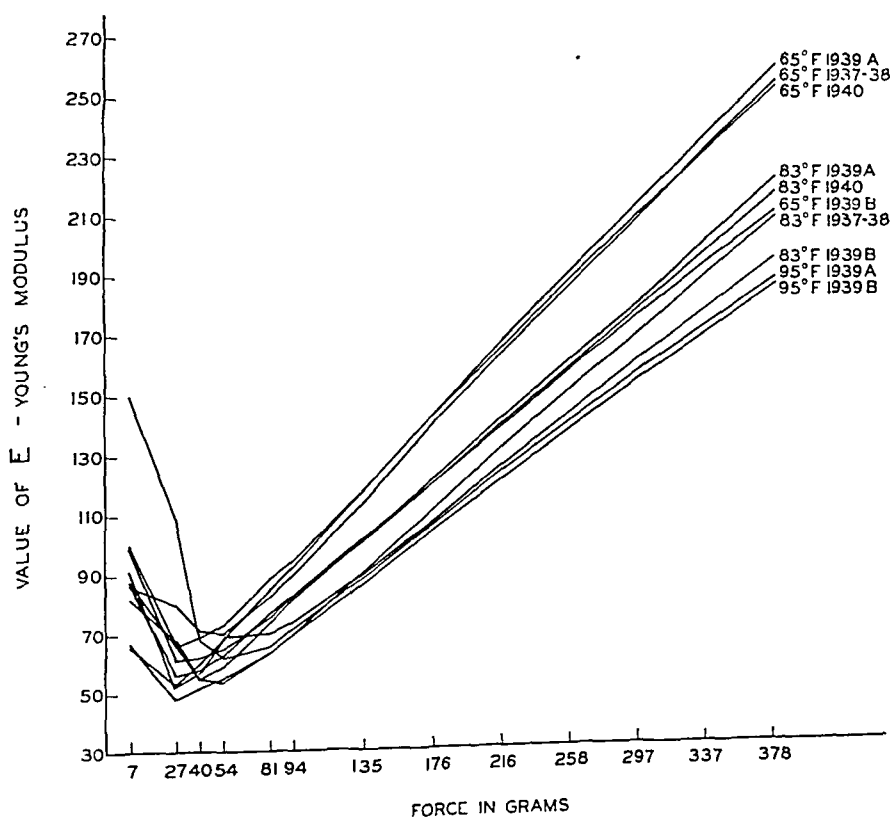


Fig. 4.—Graph of the observations after 65° F., 83° F., and 95° F. treatments. All the curves marked 1939A are from rats 120 days old; all the curves labeled 1939B are from rats 210 days old; and all the 1940 observations were made on rats 120 days old.

In the 83° F. group of 1939, the 120- and 210-day subgroups also have significantly different regressions and means. Statistically, the significance is not so great as for the pair of 65° F. observations.

In the 95° F. group of 1939, the 120- and 210-day subgroups show significant differences in means and regressions, but these differences are not so significant as the age differences within the 83° F. group, and, of course, not nearly so significant as the differences for the 65° F. observations.

As an approach to the constitutional factor which may have been introduced between the 1937-1938 experiments and those that follow, it is reasonable to ask how significantly different are 120-day groups at the same temperature in two different years if the stock is unchanged. Three comparisons are available, the 65° F. and 120-day groups for 1939 and 1940, the 83° F. and 120-day groups for 1939 and 1940, and the "disturbed" and 120-day groups for 1939 and 1940. With the same strain of animals and standard treatment for a standard length of time, these curves show the following statistical differences:

1. Means are not significantly different; regressions do differ for 65° F., 1939, 1940.
2. Means are not significantly different; regressions do differ for 83° F., 1939, 1940.
3. Means are not significantly different; regressions do *not* differ for "disturbed," 1939, 1940.

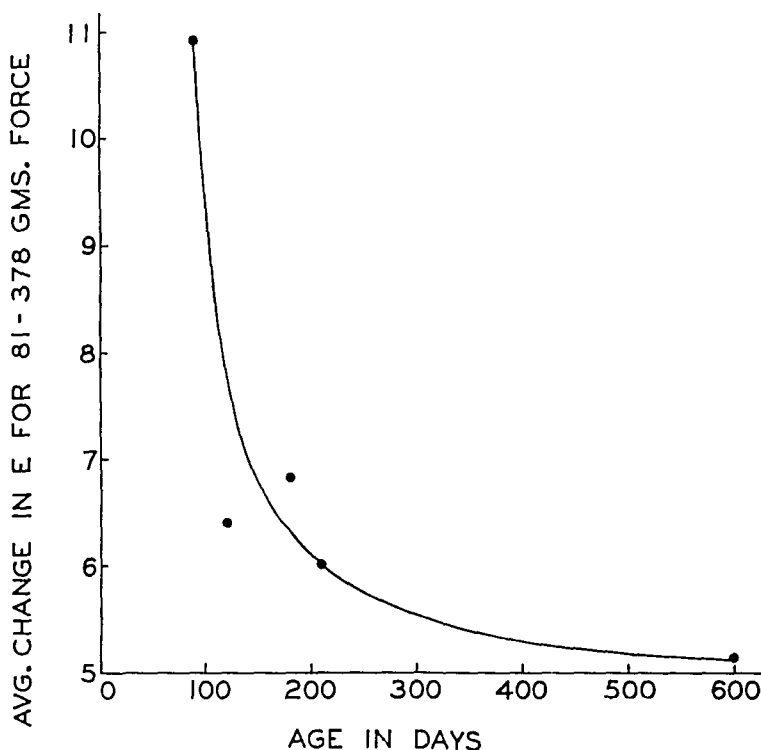


Fig. 5.—Graph of the rate of change in tensile resistance for the ascending limb of the tensility curve. The five points represent data from groups aged 90 days, 120 days, 180 days, 210 days, and 600 days. All five groups were maintained at a temperature of 82° to 84° F.

Obviously, the effect of temperature at a standard age, or of age at a standard temperature, is of a much greater order than group variability from year to year, except in the case of the age effect at high temperature, and the differential effect of medium and high temperatures at the older age of 210 days.

Such a result is entirely consistent and might be generally stated in this manner. Both age and temperature produce definite effects on the tensility curve. The effect of temperature is most pronounced at the earlier age. At the later age the distinction between high and medium environmental temperatures tends to disappear. The effect of age is most clearly seen at low and medium temperatures, whereas at the higher temperature the age effect is least conspicuous.

In these comparisons it must be remembered that the terms "age" and "temperature" refer to the conditions of these investigations and are not intended as general statements. There is, indeed, evidence from an earlier publication¹ which, in conjunction with the newer studies here reported, indicates that the age decrease in tensile resistance is progressive. In Fig. 5 we have plotted the rate of change for the ascending limb of the tensility curve, versus age in days, for data covering at least two-thirds of the rat's lifetime (90 to 600 days).

It is clear from this figure that tensility is inversely associated with age. We do not, however, know what the effect of prolonging low, medium, and high temperatures beyond 210 days may be. Fig. 5 is based upon data from animals which lived at or near the point of thermal neutrality for rats (82° to 84° F.). Since temperature has a substantial effect upon the growth of the rat, there seems to be a reason for relating the temperature effects up to the age of 210 days to general growth effects. Factors inhibiting growth (cold, alcohol) have been found to produce animals whose tensility curves resemble those of younger animals. Whether or not temperature effects may still be seen in tensility curves from animals who have attained their maximal growth, although at different rates, must be settled by further work.

Effect of Thyroid Feeding.—Any attempt to gain insight into the factors responsible for the effect of age and temperature on tensile resistance must immediately consider the rate of metabolism. It is well known that the metabolic rate of the rat is increased by temperatures either above or below the point of thermal neutrality, and that, in a gross sense, any age effect is also broadly associated with total cumulative metabolism, or rather, the sum of "rates of living" which have occurred in an organism from birth to a given age.

In an earlier paper¹ the effect of high or low temperatures in elevating the rat's rate of metabolism from a level of about 600 cal/M²/24 hours to approximately 1,000 cal. was mentioned. However, in so far as increased tensile resistance can be considered as a favorable characteristic, the cold environment is favorable and the hot environment is unfavorable. This statement involves the tentative assumption that the decreased tensility as age advances means generally that decreased tensility is "unfavorable."

This most general comparison of cold and hot environments made it clear, and it is not surprising, that the production of a high rate of metabolism by two different means does not necessarily have a common effect on the organism (effect, in this case, being judged by a property of the aorta). In short, a metabolism of the order of 1,000 cal/M²/24 hours has very different effects, depending upon whether exposure to heat or to cold is the provocative factor.

There is abundant evidence that thyroid function is increased by cold. In the temperature experiments it was reasonable to conclude that such an increase in thyroid function might be associated with cold exposure and that the increase in metabolism in hot environments was associated primarily with increased tissue temperatures. Feeding thyroid to animals exposed to a normal environmental temperature seemed indicated. In this manner, a supermetabolism caused by excess thyroxin could be induced at normal temperatures. Forty animals were fed 0.6 Gm. of desiccated thyroid extract (Lilly, U.S.P.) per 1,000 Gm. of basic ration (0.06 per cent) and maintained at a cage temperature of 83° F. These animals were sacrificed in two groups of twenty, at the age of 120 and 210 days, respectively. In so far as total metabolism is concerned, we were thus afforded a comparison between the effects of an elevated rate of metabolism induced by exposure to heat or cold and by thyroid feeding.

The effect of thyroid feeding on the tensile resistance of the rat's aorta at the age of 120 days is seen in Fig. 3. Here the curve lies below that of all groups, with the exception of the as yet undiscussed "disturbed" group. Statistically, the curve is significantly different in slope from the 65° F., the 83° F., and the "disturbed" groups, but not from the 95° F. group. In testing the means, the thyroid experiment is significantly different from the 65° F. and 83° F. groups, but not from the 95° F. or "disturbed" groups.

When a comparison is made on the 210-day group, we find essentially the same relationship. An increase in metabolism induced by thyroid feeding produces an aorta whose tensile resistance is decreased. This effect is similar to that produced by high environmental temperatures, in contrast to the effect of cold environment temperatures.

The results on thyroid-fed animals are of particular interest, for the decreased tensile resistance is not associated with retarded growth, as was the case with the 95° F. animals. Previously we¹ noted that growth inhibition produced by alcohol intoxication increased tensile resistance, and in these studies high temperature inhibition of growth produced an opposite effect. It must then be clear that the effect on aortic tensile resistance of these various treatments is no simple effect of general growth or elevated metabolism.

Effect of "Disturbance."—It has frequently been said that the "wear and tear" of modern living is related to life in an environment which is abnormally stimulating. One may assume that this statement, if it has any definite hygienic meaning, suggests that "stimulation" refers to neural factors affecting the level of nervous tension and not purposefully related to normal activity and growth.

Although it seems questionable whether or not we are prepared to create for the rat, or for any other animal, an environment in which "overstimulation" is present, in the sense in which we might understand it as a feature of high-pressure urban life, we can easily provide an environment which is noisy and physically unstable. In a previous section the apparatus used to produce noise and vibration was described. Such stimuli are almost universally effective in producing initial alarm reactions in animals. Through variation in the sequence and length of each particular stimulus in the disturbance pattern, an effort was made to provide some degree of continuous novelty in the situation. Observation showed that as far as outward signs (posture and activity) were concerned, the animals apparently adapted within a few days to the disturbing features of the environment. They interrupted their feeding at the beginning of noise or vibration, only to continue after a few moments. With vibration and high velocity of air movement, certain cage locations were "least disturbed," and animals usually congregated at these locations until the disturbance had ceased. At no time, however, could these stimuli be completely escaped in a physical sense, and it is logical to assume that the environment was "disturbed," even though dramatic evidence of such an effect on the animals rather quickly disappeared.

In Figs. 3 and 4 the comparative tensile resistance of aortas from the "disturbed" group is shown for two groups 120 days old, and one group 210 days old. In the first 120- and 210-day groups (1939 A and B) the curves of tensile resistance lie below the curves for all other groups. The change is in the direction of a decreased resistance, and, if we take young animals or animals raised in a cold environment as a reference, in an unfavorable direction. Statistically considered, the regressions of these curves are significantly different (both for 120- and 210-day observations) from any other 1939A or 1939B group, respectively. The analysis of means reveals that the "disturbed" 1939A (120 days) differs significantly from the 65° F. and 83° F. groups, but not from the "thyroid" and 95° F. groups of 1939A. At 210 days the mean difference between "disturbed" and any other 1939 group is significant or highly significant.

The results were very surprising, even though the acceptance of curves of lowered tensile resistance as unfavorable is regarded as a tentative conclusion. It is important to state that this conclusion with respect to the effect of disturbance had been reached in the 1939 experi-

ments. In order to check this result prior to publication, a new series was run in 1940 on a new group of animals. These were carried to the age of 120 days, and, in order to establish a reference point in the new series, temperature groups at 65° F. and 83° F. were run concurrently. The results are seen clearly in Fig. 2. The new curves check very well with the previous ones, both with respect to disturbance and temperature. The 1940 curve for the "disturbed" group lies at a slightly higher level than the 1939A curve, but its location in the area which is typical for other "unfavorable" treatments is obvious.

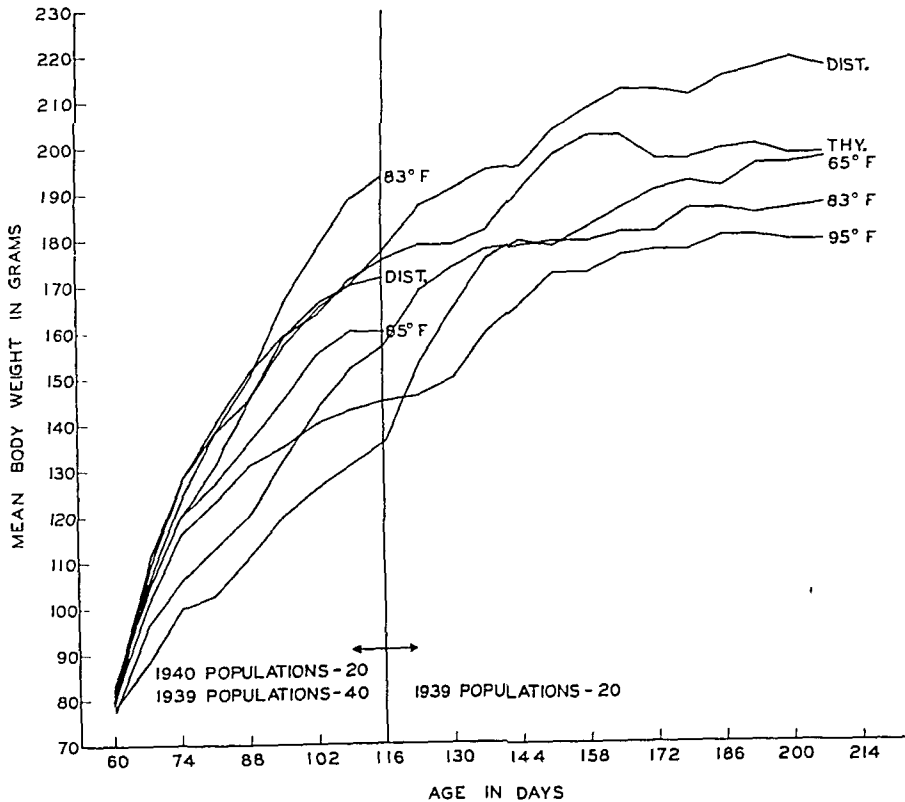


Fig. 6.—Growth curve obtained from weekly weight measurements of all 1939 and 1940 groups. Double arrow indicates age at which twenty animals from each of the 1939 groups were sacrificed.

Effect of Various Treatments on Growth.—A logical analysis of the growth curves obtained from the 1939 and 1940 studies presents several difficulties. The main difficulty lies in the fact that the curves from 60 to 120 days represent the average weight of forty animals, whereas from 120 to 210 days the average weights are based on twenty animals. Thus, there is an increased variability in the second half of the curves which is related to the smaller number of animals. It is clear that, by reducing the crowding of occupants of a cage (from forty to twenty animals), a generally favorable effect has resulted which we had not anticipated. The precise nature of this influence is obscure, for all groups were given an abundance of food. We can avoid any prejudicial

effect of this variable by discussing the two sections of the curves separately. In Fig. 6 the growth curves of all 1939 and 1940 groups are given, after smoothing, with a moving average of three.

In the period from 60 to 117 days it seems improbable that there was any decided difference in growth rate for the three 1939 temperature groups. Such differences as exist suggest that high or moderate temperatures may be advantageous for growth in the early part of the period; this effect becomes less marked as the animal increases in size, and is finally reversed in adulthood. The removal of twenty animals from the cage resulted in an immediate increase in growth rate in the 1939 temperature groups, and the absence of such a marked effect in the "thyroid" and "disturbed" groups suggests that these rapidly growing animals are nearer their physiologic limit of increase, and hence least susceptible to the effect.

We were able to check this "crowding" effect with 1940 data, in which we have the growth curves for twenty animals in the period from 60 to 117 days. As may be readily seen in Fig. 6, these groups grew much more rapidly than the 1939 groups, which comprised forty animals.

In the second age period, 117 to 210 days, the 1939 temperature curves reverse themselves, and, at the final period (210 days), the heaviest animals are those from a cold environment, the lightest, those from the hot environment, and the moderate temperature group occupy the middle rank in weight.

One is tempted to say that in an experiment uncomplicated by any change in cage population, the effect of temperature up to 120 days would probably be a relative inhibition of growth in the cold (see 1940 results also), in contrast with final adult results, in which cold is favorable and heat unfavorable for growth, as measured by weight.

Somewhat to our surprise, the growth curves for the "disturbed" and "thyroid" groups were consistently above the temperature groups, and the crowding effect was not noticeable, either when the cage populations were reduced to twenty, or when the first growth period was checked for the "disturbed" in 1940 with only twenty animals. This suggests that the rates of growth shown for the "disturbed" and "thyroid" were already near a maximum for this strain of rat and the particular diet used.

Both "thyroid" and "disturbed" animals gave group results on the arterial tests in 1939 and 1940 which were "unfavorable"; in other words, in the direction of the effect produced by high temperatures and increasing age. These growth results immediately suggest that perhaps the "thyroid" and "disturbed" were physiologically older as a result of their more rapid growth and that the "unfavorable" arterial performance of these groups was really an age artifact. This conclusion is untenable, however, when it is remembered that the "thyroid" and

TABLE III
1939 GROWTH DATA

1 EXPERIMENT NO.	2 AGE (DAYS)	3 SPECIAL TREATMENT	4 AV. FINAL WEIGHT (GM.)	5 INITIAL WEIGHT (GM.)	6 AV. GAIN IN WEIGHT (GM.)	7 AV. GAIN IN WEIGHT 120-210 DAYS (GM.)	8 WEIGHT- LENGTH RATIO	9 ORDER OF W/L RATIO	10 AV. LENGTH (CM.)	11 AV. GAIN IN LENGTH 120-210 DAYS (CM.)
9	120	65° F.	145	72	60-120 days 73		8.80	120 days 3	120 days 16.7	
10	120	83° F.	155	79	76		8.60	5	18.1	
11	120	95° F.	150	80	70		8.76	4	17.0	
12	120	Thyroid	188	79	109		9.66	1	20.0	
13	120	Disturbed	176	81	95		8.88	2	19.8	
14	210	65° F.	217	72	60-210 days 145		10.29	210 days 2	210 days 20.1	3.4
15	210	83° F.	204	79	125		10.24	3	19.9	1.8
16	210	95° F.	184	80	104		9.48	5	19.4	2.4
17	210	Thyroid	204	79	125		9.82	4	20.8	0.8
18	210	Disturbed	223	81	142		10.90	1	20.4	0.6

65° F. animals had very nearly the same final growth status and that the arterial results for the "cold" animals were quite in the other direction.

It is probably sufficient to note that conditions which are unfavorable from the standpoint of arterial tests are not necessarily associated with retarded growth. Obviously, the effects are subject to the influence of many variables, and the basic physiologic interrelations are not simple.

Inclusion of length and weight-length ratio adds another dimension to the picture of the effect of the various treatments on growth. This discussion will be limited to the five groups studied in 1939 because of the continuity from 60 days to 210 days. It will be seen from Table III that, at 120 days, the "thyroid" group had attained the greatest length, with the "disturbed," 83° F., 95° F., and 65° F. following behind in that order. At 210 days, "thyroid" and "disturbed" were still the longest animals, but 65° F. had moved up from fifth to third place, 83° F. had moved from third to fourth place, and 95° F. from fourth to fifth place. This shift in order is significant, and will be discussed shortly. At 120 days, "thyroid" had the highest ratio, with "disturbed," 65° F., 95° F., and 83° F. following in descending order. At 210 days the "disturbed" group had the highest ratio, with 65° F., 83° F., "thyroid," and 95° F. in the same order. The treatments to which the animals were exposed are clearly reflected in the length-weight ratio of the different groups; weight alone is an incomplete criterion of growth because length as well as weight is affected by treatment.

A closer analysis reveals that the average length of the "thyroid" group, as might be expected, was greatest both at 120 days and at 210 days. At 120 days, it also had the highest weight-length ratio, which shows that it was also the heaviest group. At 210 days, however, the "thyroid" weight-length ratio had dropped from first to fourth place, indicating that the increment of weight had not kept pace with the increment in length, and that the thyroid treatment was producing proportionately longer, thinner rats. It is startling that, from 60 to 120 days, the "thyroid" animals gained 109 Gm., on the average, whereas from 120 to 210 days the average gain was only 16 Gm. The growth curve corroborates the fact that there was very rapid growth in the first 60 days of treatment, with a decided slowing down in the next 120 days. The increase in length from 120 to 210 days seems very small (8 mm.), but it is actually a little in excess of the comparative figures given by Donaldson for change in length with change in body weight.

The "disturbed" animals, at 120 days, had the second highest weight-length ratio, and were the second longest. Therefore, they were also the second heaviest. At 210 days the weight-length ratio was highest, although the length remained in second place. Therefore, the gain in

weight was greater than the gain in length. From 60 to 120 days the average gain in weight was 95 Gm., as compared to 109 for the "thyroid." The contrast between the two groups came in the weight gain attained between 120 and 210 days. Although the "thyroid" gained but 16 Gm. on the average, the "disturbed" gained 47 Gm. In length, the "disturbed," like the "thyroid," gained very little from 120 to 210 days. Most of the weight and length growth in both of these groups was attained early, i.e., between 60 to 120 days.

The three temperature groups behaved somewhat differently. The average gain in weight between 60 and 120 days for the 65° F. group was 73 Gm., which is considerably less than the gain made by either the "thyroid" or "disturbed" groups for the same period, but the gain between 120 and 210 days amounted to 72 Gm. Thus, the total weight gain from 60 to 210 days was slightly more than for any other group, but the important difference is that it was evenly distributed over the period from 60 to 210 days. The weight-length ratio for the 65° F. group at 120 days was third highest; these animals showed the shortest lengths of any group. At 210 days the weight-length ratio had moved up to second place, and the length was also increasing. Thus, the growth of the 65° F. groups was one of even, steady gains, both in weight and length. The largest gains of any group from 120 to 210 days in both measurements were attained by this group. The average increase in length between 120 and 210 days was 34 mm.

The 83° F. groups, which served as the controls for all the others, tended to strike a mean between the behavior of the 65° F. and the "thyroid" and "disturbed" groups. At 120 days the weight-length ratio was the smallest, the length was third greatest, and the weight was the third highest of all the groups. At 210 days the weight-length ratio moved up to third place, indicating a somewhat greater increase in weight in proportion to length. The weight gain averaged 76 Gm. for the 60- to 120-day period, and forty-nine for the 120- to 210-day period. The increase in length between 120 and 210 days averaged 18 mm., which amounted to about half of the gain achieved by the 65° F. group, but twice to three times as much as was gained by the "thyroid" and "disturbed" groups, respectively. The effect of an even, medium temperature seemed to combine the effects of stimulation by thyroid feeding and by a cold temperature. There was more gain in weight early in the experiment than in the latter portion; the rate of increase in length continued during this period, but was not out of proportion to the weight gain.

Finally, the effect of a hot environmental temperature was to produce an animal whose length was proportionately greater than its weight at all times. The weight-length ratios at 120 and 210 days were next to smallest and smallest, respectively, of any of the groups. The average

weight gain from 60 to 120 days was 70 Gm., but was only 34 Gm. from 120 to 210 days, whereas the increase in length during the latter period was 24 mm., or next to the highest. Most of the weight gain took place in the early part of the experiment, but the increase in length continued at a high level throughout.

A brief summary of the 1939 growth experience, as judged by weight, length, and weight-length ratios, shows that the treatment to which each group was subjected had a definite effect, not only on the final level reached, but also on the rate of growth during the experiments. As judged by the "final level" criterion, the "disturbed" group was the heaviest and second longest; the "thyroid," the third heaviest and longest; the 65° F. group, the second heaviest and third longest; the 83° F. group, the fourth heaviest and fourth longest; and the 95° F. group, the lightest and shortest. The rates of change indicate that the "thyroid" group did most of its growing between 60 and 120 days, as did the "disturbed" group. Of the three temperature groups, the 65° F. grew more between 120 and 210 days, and the 83° F. and 95° F. followed at a slower pace.

GENERAL DISCUSSION

To supplement the graphs already presented, we have prepared (Table IV) a summary of the outstanding differences in the total of twenty-one experiments which were carried out between 1937 and 1940. The first five columns record the basic variables, i.e., temperature, special treatment, and age of animals for each experiment. The sixth column gives the mean weight of the animals at the close of each experiment, and the last three columns show values for Young's modulus at three significant points. Column 7 is the initial reading, with a weight of only 7 Gm. Column 8 is the average reading (with weights of 27 to 54 Gm.) at the low point of the curve, where the modulus reaches its minimum value. Column 9 is the reading corresponding to a weight-stress of 378 Gm., where the modulus is close to its maximum.

In general, the modulus for comparable conditions (like the ultimate breaking point) was higher in 1937-1938 than in later experiments (this was caused either by a difference in stock or by some unidentified difference in experimental procedure). The change of final modulus (378 Gm.), with age, in this earlier series was from 370 at 90 days to 250 at 180 days and 184 at 600 days (all at 72° to 73° F.). At 210 days the value at 65° F. was higher (257) than at 82° F. or 90° F. (211 to 215). Lead and alcohol exposure at 82° F. seemed, as pointed out in an earlier communication,¹ to be associated with a higher modulus than that characteristic of control animals of the same age at 72° F., or than that of control animals of the same weight after 210 days at 82° F.

TABLE IV
GENERAL SUMMARY

1 EXPERIMENT NO.	2 DATE	3 TEMPERATURE OF CAGE (° F.)	4 SPECIAL TREATMENT	5 AGE (DAYS)	6 AV. WT. AT- TAINED AT END OF EXPERIMENT (GM.)	7 YOUNG'S MODULUS		
						INITIAL (7 GM.)	LOW POINT (AV. 27-54 GM.)	HIGH POINT (378 GM.)
1	1937-38	72-73*		90		178	98	370
2	1937-38	82	Lead	180	256	181	72	291
3	1937-38	72-73*		180	287	127	60	250
4	1937-38	82	Alcohol	180	217	89	60	272
5	1937-38	65		210	193	86	74	257
6	1937-38	90		210	230	88	58	211
7	1937-38	82		210	260	74	59	215
8	1937-38	72-73*		600	400	85	42	184
9	1939A	65		120	145	66	60	262
10	1939A	83		120	155	82	60	224
11	1939A	95		120	150	150	79	190
12	1939A	83	Thyroid	120	188	198	119	189
13	1939A	83	Disturbed	120	176	96	52	172
14	1939B	65		210	217	99	63	213
15	1939B	83		210	204	91	56	197
16	1939B	95		210	184	67	52	188
17	1939B	83	Thyroid	210	204	82	43	174
18	1939B	83	Disturbed	210	223	50	38	168
19	1940	65		120	168	100	69	255
20	1940	83		120	203	87	59	219
21	1940	83	Disturbed	120	170	70	50	195

*Uncontrolled.

The last thirteen experiments, which were conducted in 1939-1940, are mutually comparable, for they were done with animals of uniform stock. They confirm the earlier conclusions that Young's modulus decreases with age, and, at a given age, with an increase in environmental temperature. It is important to know, however, whether the influence of low temperature in maintaining a high value at a given age is due merely to a slowing up of growth processes or to some directly favorable effect upon the state of the arteries. In Fig. 7 we have plotted all the 1939-1940 experiments to show the relation of the modulus value to the mean weight of the animals, irrespective of age. In every case, however, the final point in each curve represents a 210-day group. All other points are for 120-day groups. It will be noted from the graph that all curves show a tendency to fall with increasing age and weight and that, for a given age and weight, the animals which were kept at a temperature of 65° F. showed a higher modulus than those kept at 82° F., whereas the animals kept at 95° F., as well as those overstimulated by thyroid feeding or sensory disturbance, all showed a modulus lower than normal.

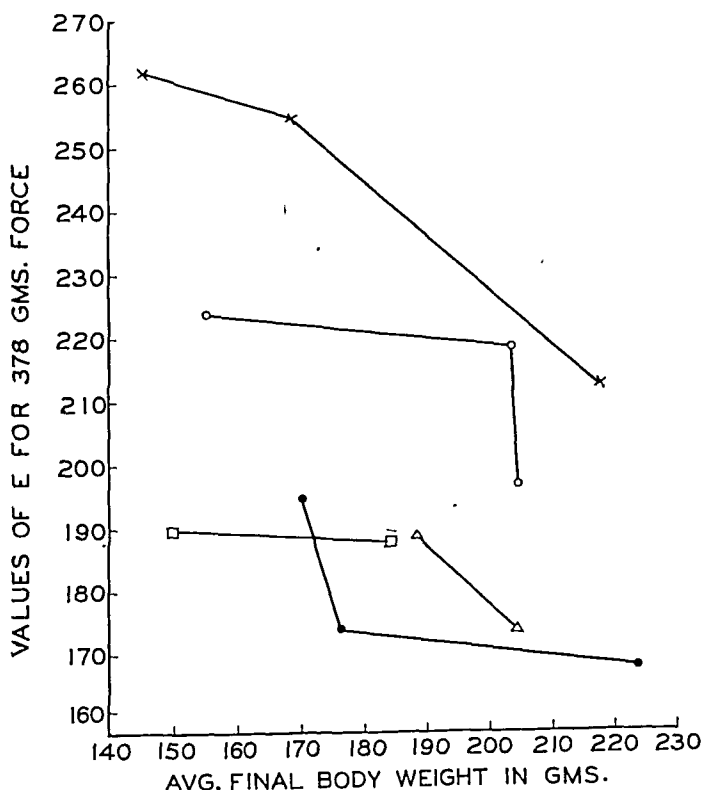


Fig. 7.—Graph of average body weight, versus values of E at a weight of 378 Gm. for various treatment groups, irrespective of age. Crosses (x) are for groups at 65° F.; open circles (o), for groups at 83° F.; open squares (□), for groups at 95° F.; triangles (Δ), for thyroid-treated groups; solid circles (●), for "disturbed" groups. Points plotted represent both 120- and 210-day results; it so happens, however, that the lowest point in each series is a 210-day group; all other points are for 120 days.

Little has been said about the initial limb of the tensility curve or the low point of the modulus, because it is clear that the slope and placement of the long, ascending, right limb of the curve for a given group

afford the most reliable and characteristic measure of the performance of the artery on the tensometer. Since the stresses involved were well beyond physiologic limits, it is believed that the right limb measures a structural property. It can be seen readily from Table IV, however, that the initial and low modulus values which define the descending curve are, in general, proportional to the final values at 378 Gm. of stress. These initial and low values lie in a stress range which is within physiologic limits. It therefore seems reasonable to conclude that there is a fairly substantial relationship between the structural property, as measured by the ascending limb, and the tensile resistance of the arterial section in the range of physiologic stress which is involved in the initial section of the curve. There are, however, certain rather conspicuous exceptions to the general association between the initial, low, and final values. Groups 11 and 12 (Table IV), respectively the 120-day, 95° F. and 120-day, "thyroid" groups, gave exceptionally high initial values in association with low final values. Both of these groups had experienced rapid early growth, although it should be noted that this tapered off in the 95° F. group between the ages of 80 and 100 days. This is not unusual, for there are sound reasons for believing that the optimal temperatures for growth are higher in the early stages of development than in the later stages. This is shown by the reversal of the position of the growth curves in the 1939 experiments at 88 and 210 days. At 88 days the temperature groups, in the order of greatest weight, were 95°, 83°, and 65° F. At 210 days this order became reversed, and we find the highest level of growth in the 65° F. group, with the 83° and 95° groups following in that order.

Group 9, the 120-day, 65° F. animals, deviated from the general trend of association between initial and final values for the modulus in a direction opposite from that noted for Groups 11 and 12. Group 9 grew more slowly than any other group up to 120 days. These three conspicuous deviations from the general trend may be fortuitous, but it should be noted that these deviations between initial and final values in Table IV concern groups in which conspicuously high or low initial values were associated, respectively, with accelerated or retarded growth at the age of 120 days.

CONCLUSIONS

1. The tensility of the aorta of the rat, as measured by the Hume tensometer, appears to be a valid measure of certain processes of aging in the arterial wall. With advance in both actual and physiologic age (as measured by weight increase), the tensile resistance of the aortic rings to distention stresses shows a progressive decrease.

2. The aortas of rats maintained at an air temperature below normal (65° F.) show a higher tensile resistance than those of rats of the same

age and weight maintained at a temperature of 83° F. This phenomenon is, of course, associated with an increased rate of metabolism.

3. Rats maintained at 95° F., or at 83° F. with regular doses of thyroid extract, show a high metabolic rate which is comparable to that produced by a temperature of 65° F. Yet, in such rats, the tensile resistance of the aorta, instead of being increased, is decreased to a value below that of the 83° F. controls.

4. Rats exposed to repeated sensory disturbances show a similar reduction of tensile resistance; their aortic wall yields to stress more readily than that of control animals of corresponding age and weight, kept at the same normal temperature of 83° F.

REFERENCES

1. Hume, Jean: The Tensility of the Rat's Aorta as Influenced by Age, Environmental Temperature, and Certain Toxic Substances, *Am. J. Hyg.* 29: 11, 1939.
2. Fleisch, A.: Structure of Blood Vessels, *Bethe Handb. d. normalen u. path. Physiol.* 7: 865, 1927.
3. Clark, J. H.: Elasticity of Veins, *Am. J. Physiol.* 105: 418, 1933.
4. Landauer, W.: Thyroid Activity and Environmental Temperature in Frizzle Fowl, *Arch. internat. de pharmacodyn. et de therap.* 49: 130, 1934.

DIGITALIS AND THE NORMAL WORK ELECTROCARDIOGRAM

IRVING M. LIEBOW, M.D., AND HAROLD FEIL, M.D.
CLEVELAND, OHIO

DURING the course of routine interpretation of electrocardiograms in this laboratory, the record of a digitalized patient who had undergone an exercise tolerance test was encountered. The record after exercise, but not before, showed depression of the S-T junctions. This was thought to substantiate the clinical diagnosis of angina pectoris. The question was raised, however, as to whether or not digitalization alone might affect the work electrocardiogram, and a search of the literature revealed only one reference to the subject. Zwillinger,¹ in 1935, attempted to correlate the similarity of electrocardiographic changes in cases of digitalized controls with the electrocardiographic changes in subjects with proved coronary artery sclerosis during attacks of angina pectoris. He took electrocardiograms of four young, normal adults before and after exercise and repeated the test after digitalization. He noted that the administration of digitalis produced in some cases a work electrocardiogram with depression of the level of the S-T take-off. The resulting electrocardiograms resembled those from patients during attacks of angina pectoris, although Zwillinger's subjects were normal.

This is an important observation. Furthermore, since this was the only report we could find in either American or foreign journals, and since Zwillinger's observations were made on only a small number of subjects (four), it was considered of interest to repeat the work.

METHOD

Fourteen volunteers were used in the experiment. All were males, and the ages of thirteen of them ranged from 25 to 31 years; the fourteenth was 51 years of age. All were in good health so far as could be ascertained.

An electrocardiogram was made of each subject while at rest. He was then asked to make 100 trips over two steps. Each of these steps was 9 inches high, and a trip consisted of climbing the two steps to a small platform and then descending the opposite side. The subject then faced about, re climbed and redescended the steps, making a second trip—and so on, until 100 trips were completed without rest. He proceeded at his own rate. Immediately after completion of the 100 trips, a second electrocardiogram was taken. The subject was then digitalized, and the process was repeated.

From the Department of Medicine, Western Reserve University, and the Lakeside Hospital, Cleveland.

Received for publication March 12, 1941.

TABLE I
EFFECT OF EXERCISE ON LEVEL OF S-T JUNCTION

NO.	SUBJECT	BEFORE DIGITALIS				AFTER DIGITALIS			
		I	II	III	IV	I	II	III	IV
1	H. F.	0 to +	0 to 0	- to -	+ to +	0 to 0	- to -	- to -	0 to 0
2	S. R.	0 to 0	+ to 0	+ to -	+ to +	0 to 0	0 to -	0 to -	+ to 0
3	W. M.	0 to -	- to -	- to -	0 to 0	0 to -	- to -	- to -	0 to 0
4	M. B.	- to -	0 to -	+ to 0	0 to +	- to -	- to -	0 to -	- to -
5	K. R.	+ to 0	+ to +	+ to +	+ to +	0 to -	+ to -	0 to -	+ to 0
6	I. L.	+ to 0	+ to 0	0 to 0	+ to +	+ to -	+ to -	0 to -	+ to +
7	L. B.	0 to 0	+ to -	0 to -	+ to -	0 to -	0 to -	0 to -	+ to -
8	R. G.	0 to 0	0 to 0	0 to 0	+ to +	0 to 0	+ to 0	0 to 0	+ to 0
9	H. P.	0 to -	0 to -	0 to -	+ to +	- to -	0 to -	0 to -	0 to -
10	J. M.	+ to 0	+ to 0	0 to 0	+ to +	+ to -	0 to -	0 to -	+ to +
11	C. B.	0 to 0	0 to 0	0 to 0	0 to 0	- to -	0 to -	0 to -	- to -
12	W. P.	0 to 0	+ to 0	+ to 0	0 to 0	0 to 0	0 to -	+ to +	- to -
13	A. P.	0 to 0	0 to 0	0 to 0	+ to +	0 to -	+ to 0	0 to +	+ to 0
14	R. E.	0 to 0	+ to 0	0 to -	+ to +	0 to 0	0 to -	+ to -	+ to -

The subjects were digitalized by the administration of 0.1 Gm. tablets of digitalis folia. The individual total doses ranged from 1.5 to 3.4 Gm., and the time consumed in effecting digitalization, in thirteen cases, ranged from two to four and one-half days. The fourteenth person was digitalized in eighteen hours. The symptoms denoting full digitalization were the usual yellow vision, anorexia, nausea, abnormal sensation in the epigastrium ("pressure," "flutter," "uneasiness," "fullness," "excited feeling"), bradycardia, and lightheadedness. In one instance there were no subjective symptoms; only a marked bradycardia was noted. Electrocardiographic evidence of a digitalis effect was present in very few instances, and then only to a minor degree.

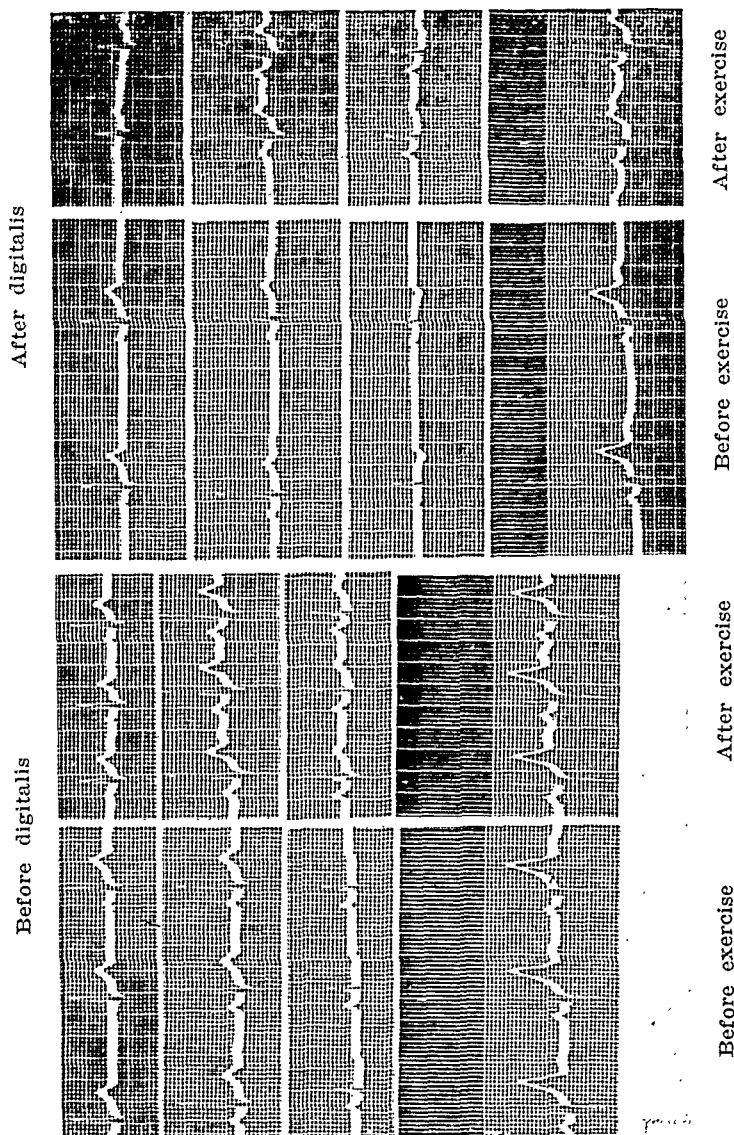


Fig. 1.

RESULTS

The outstanding change following exercise, after digitalization, was the general depression of the S-T junction. This, contrasted with the absence of such depression after exercise in the undigitalized subjects, is well illustrated in Table I. Indeed, in four subjects the deviation

of the S-T junction was greater than 1 mm. below the isoelectric line, which is generally accepted as distinctly abnormal.² Such changes are pictured in Figs. 1 and 2. This degree of depression of the S-T junction

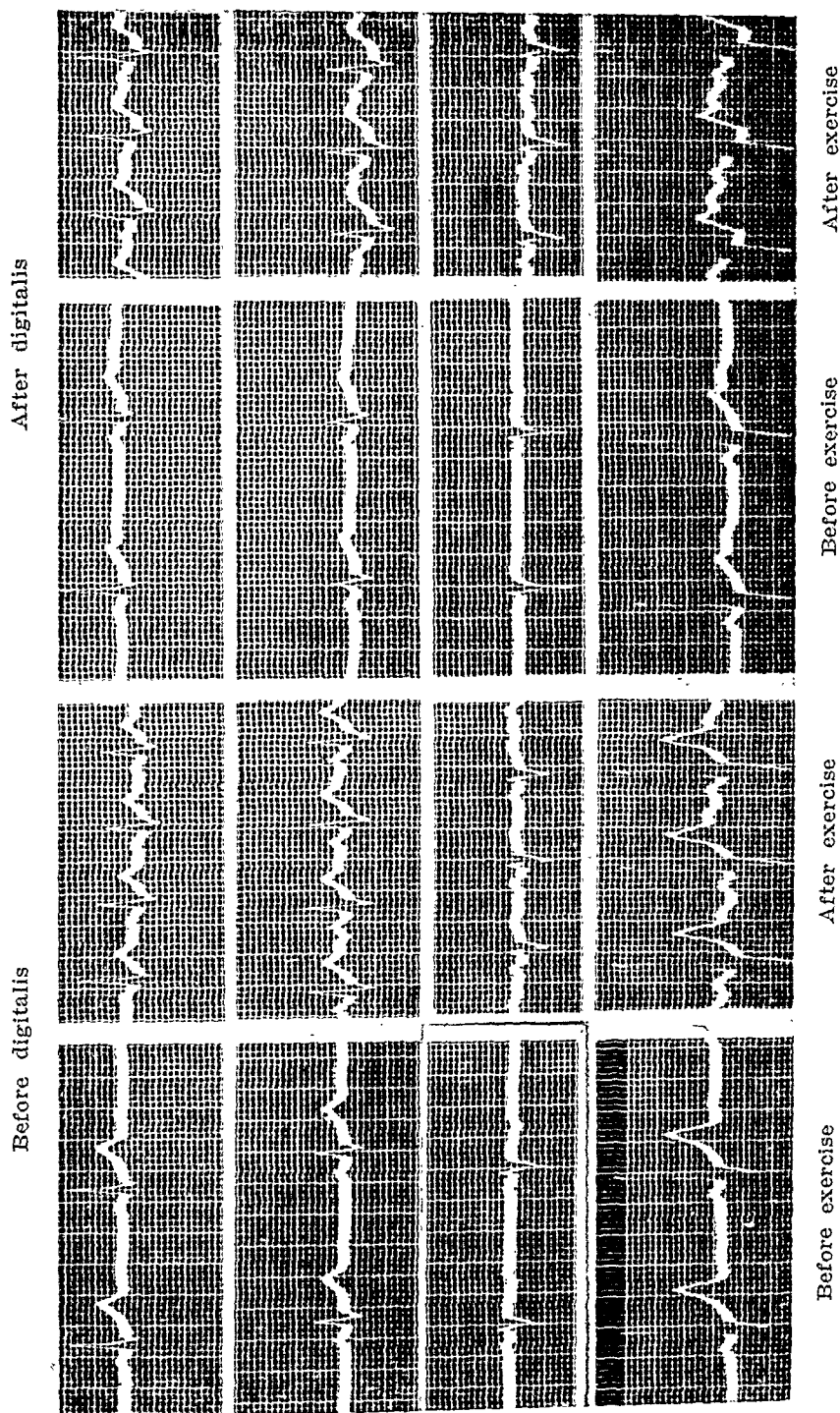


Fig. 2.

was never encountered in the undigitalized subjects. The changes may be compared with those which occur in a patient with coronary artery sclerosis before and during an attack of angina pectoris (Fig. 3).

After digitalization, exercise did not cause upright T waves to become inverted, but in four subjects an upright T wave became diphasic. Be-

fore digitalization, exercise had had a different effect. It caused an increase in the amplitude of the T waves in three of the subjects, and slight flattening in the fourth. In five subjects digitalization caused an upright T_s to become diphasic, and after exercise the diphasic waves became completely inverted. Before these subjects were digitalized, exercise had caused slight flattening of T_s in three instances, no change in one instance, and an actual increase in amplitude in the remaining case. Similarly, in one subject, records taken before exercise, both before and after digitalization, showed a diphasic T_s ; before digitalization exercise caused the T wave to become upright, whereas after digitalization the diphasic wave developed a greater negative component.

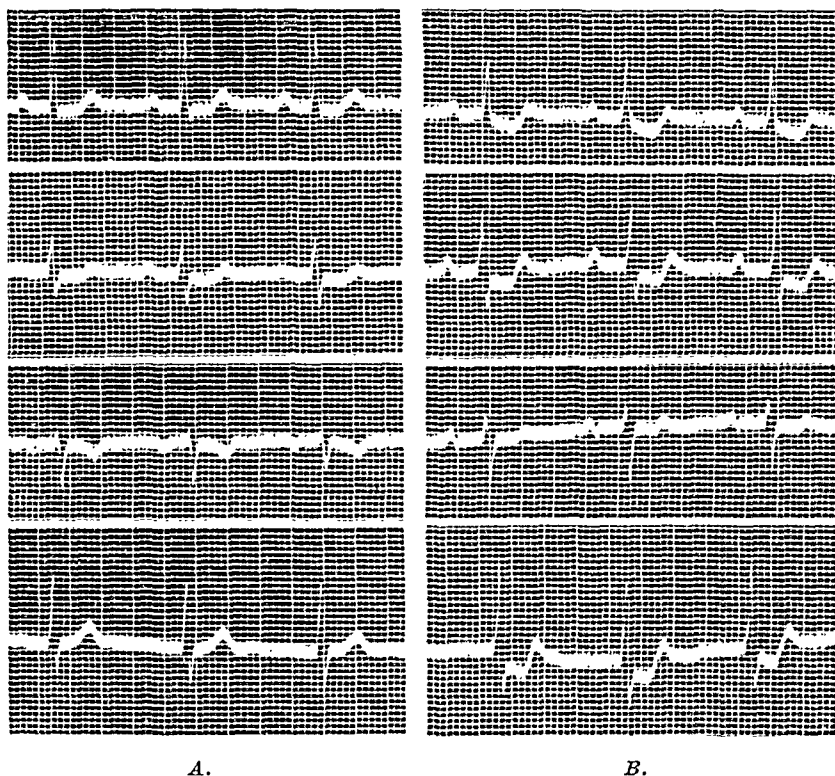


Fig. 3.—A. Patient at rest, without pain. B. Patient during attack of angina pectoris.

In two subjects exercise after the administration of digitalis was followed by relatively long periods of sinus arrest. In one record the R-R interval was 0.64 second, and the period of sinus arrest lasted 1.4 seconds; in the other the R-R interval was 0.72 second, and the period of asystole was 1.24 seconds. In the latter case P_s became markedly inverted, although it had remained upright in the control.

COMMENT

It has been known for some time that electrocardiographic changes are associated with some attacks of angina pectoris. Feil and Siegel,³ Parkinson and Bedford,⁴ and Hall⁵ have shown that with induced

attacks of pain there are depression of the S-T junction and diminution in the amplitude or inversion of the T waves in one or more leads. Wood and Wolferth⁶ observed the same changes with both spontaneous and induced attacks. These facts have been put to clinical use in the diagnosis of angina pectoris. In a doubtful case an electrocardiogram is taken and the patient then exercises until pain is induced. An electrocardiogram is taken immediately to ascertain what changes have appeared. It is of great importance, therefore, that no factor other than the state of coronary flow affect the work electrocardiogram. We have shown that digitalization will produce, in a certain proportion of normal persons who experienced no pain, changes in the S-T junction and the T wave of the work electrocardiogram that resemble those in records taken during spontaneous or induced attacks of angina pectoris. Therefore, a check should be made in all cases concerning digitalis administration.

The question arises as to why digitalis causes such changes. The effect of this drug on the coronary arteries is still not known. Work on arterial strips, heart-lung preparations, and intact animals has yielded very different results. Gilbert and Fenn⁷ found that digitalis bodies may exert a vasoconstrictor action; Essex, Herriek, and Visscher⁸ observed no effect on the mean coronary flow; and Ginsberg, Stoland, and Siler⁹ found a constrictor effect which they considered inconsequential. There is agreement, however, on the changes that occur in the electrocardiogram following anoxemia. Rothschild and Kissin¹⁰ observed S-T deviation in both normal subjects and (particularly) people with angina pectoris during induced general anoxemia. Katz, Hamburger, and Schutz¹¹ observed flattening of T, occasional inversion of T in Lead III, and a downward shift of the S-T segment in normal subjects during generalized anoxemia. Levy, Barach, and Bruenn¹² reported slight flattening of T waves and a little depression of the S-T segments in normal subjects who breathed a low-oxygen mixture; in patients who had heart disease with cardiac pain, the anoxemia was associated with a change in amplitude, and occasionally in direction, of the T wave, and appreciable depression of the S-T segments. These changes caused by generalized anoxemia, particularly in patients with an impaired coronary circulation, are similar to those which occur in digitalized normal persons after exercise. It seems possible, then, that the oxygen supply to the heart during exercise is less after digitalization than in the undigitalized state.

SUMMARY

1. Exercise electrocardiograms were made of fourteen normal persons before and after digitalization.

2. When the subjects were digitalized, exercise caused a general depression of the S-T junction which in four instances was distinctly abnormal. Changes in T waves and rhythm also occurred.

3. It is therefore imperative that the digitalis effect on work electrocardiograms be not confused with work electrocardiograms which show the result of myocardial ischemia due to coronary artery disease.

REFERENCES

1. Zwillinger, L.: Die Digitaliseinwirkung auf das Arbeits-Elektrokardiogramm, *Med. Klin.* 30: 977, 1935.
2. Feil, H.: The Chest Lead Electrocardiogram in Chronic Cardiac Anoxemia, *Am. Assoc. Adv. Sc., Publication No. 13*: 163, 1940.
3. Feil, H., and Siegel, M. L.: Electrocardiographic Changes During Attacks of Angina Pectoris, *Am. J. M. Sc.* 175: 255, 1928.
4. Parkinson, J., and Bedford, D. E.: Electrocardiographic Changes During Brief Attacks of Angina Pectoris; Their Bearing on the Origin of Anginal Pain, *Lancet* 1: 15, 1931.
5. Hall, D.: Electrocardiograms of Two Patients During Attacks of Angina Pectoris, *Lancet* 1: 1254, 1932.
6. Wood, F. C., and Wolferth, C. C.: Angina Pectoris, *Arch. Int. Med.* 47: 339, 1931.
7. Gilbert, N. C., and Fenn, G. K.: Effect of Digitalis on the Coronary Flow, *Arch. Int. Med.* 50: 668, 1932.
8. Essex, H. E., Herrick, J. F., and Visscher, M. B.: Influence of Certain Glucosides of Digitalis Lanata on the Coronary Blood Flow and Blood Pressure in the Trained Dog, *AM. HEART J.* 16: 143, 1938.
9. Ginsberg, A. M., Stoland, O. O., and Siler, K. A.: Studies on Coronary Circulation. VI. The Effect of Some Members of the Digitalis Group on the Coronary Circulation, *AM. HEART J.* 16: 663, 1938.
10. Rothschild, M. A., and Kissin, M.: Induced General Anoxemia Causing S-T Deviation in the Electrocardiogram, *AM. HEART J.* 8: 745, 1933.
11. Katz, L. N., Hamburger, W. W., and Schutz, W. J.: The Effect of Generalized Anoxemia on the Electrocardiogram of Normal Subjects. Its Bearing on the Mechanism of Attacks of Angina Pectoris, *AM. HEART J.* 9: 771, 1934.
12. Levy, R. L., Barach, A. L., and Bruenn, H. G.: Effects of Induced Oxygen Want in Patients With Cardiac Pain, *AM. HEART J.* 15: 187, 1928.

MYOCARDIAL NECROSIS IN DIPHTHERIA

WITH A GENERAL REVIEW OF THE LESIONS OF THE MYOCARDIUM IN
DIPHTHERIA

K. Y. CH'IN, M.D., AND C. H. HUANG, M.D.
PEIPING, CHINA

DEATH of diphtheria patients from circulatory failure is a well-known and frequent occurrence, but the cause of the circulatory failure has been variously explained by different writers. Certain authors regard the cause as extracardiac. Romberg, et al.,¹ found that mechanical expression of blood from the splanchnic veins or compression of the aorta restored the heart's action in rabbits poisoned with diphtheria toxin, and considered that the heart failure was due not to myocardial damage but to a fall of blood pressure which they believed to be the result of poisoning or paralysis of the vasomotor center in the brain. Brodie,² experimenting with cats, thought that the cardiac death was caused by failure or relaxation of the blood vessels and the consequent fall in blood pressure, and Friedmann³ regarded the diphtheria toxin as a specific poison for the blood vessels or the peripheral vasomotor nerves. MacCallum,⁴ by artificially increasing the blood pressure in the aorta and by perfusing isolated hearts, found that the hearts from diphtheria-poisoned dogs could be made to continue or resume beating for hours by such means after circulatory collapse, or even death, had occurred. Thus it is generally conceded that circulatory failure in diphtheria may be a result of vasomotor paralysis without demonstrable myocardial damage. This is particularly true in cases in which death from circulatory failure occurred in the acute stage of the disease.

Again, certain authors attribute the cardiac failure to peripheral nerve degeneration. Veronese⁵ found degeneration of the vagus, the cardiac ganglion, and the sympathetics, and maintained that this was the cause of the heart failure. Vincent⁶ also regarded the vagal injury as essential. Thomas and Hibbard⁷ concluded from their histologic studies of the nervous and myocardial lesions in diphtheria that the changes in the nerves were observed earlier and with greater constancy, and were therefore of greater importance than the myocardial degeneration, which they thought was secondary to vagal injury. On the other

From the Departments of Pathology and Medicine, Peiping Union Medical College.
Received for publication March 28, 1941.

hand, Leyden,⁸ Unruh,⁹ Huguenin,¹⁰ and Hochhaus¹¹ were unable to demonstrate any changes in the vagi and cardiac ganglia that they studied.

Abramow¹² found experimentally that large doses of diphtheria toxin caused suppression of the suprarenal secretion, and he ascribed the circulatory collapse in diphtheria to adrenal insufficiency.

That damage to the myocardium itself was also present was shown by MacCallum's⁴ observation that the hearts of diphtheria-poisoned dogs did not continue to beat as long as the control hearts, were feeble in action, and showed a tendency to fibrillation, and by the electrocardiographic changes observed by a great many investigators (Nathanson,^{13, 14} Begg,¹⁵ Thompson, et al.,¹⁶ Perry,¹⁷ Boyle, et al.¹⁸) in diphtheria patients and in animals poisoned with diphtheria toxin. However, as regards the pathologic nature, the site, and the extent of the myocardial damage, and the significance of the myocardial lesions in relation to the cause of death, there exists much difference of opinion. MacCallum¹⁹ and Donnerstag²⁰ found that the gross and microscopic changes in the heart were scarce and insignificant, and Loth²¹ stated that the lesions were usually only cloudy swelling and focal fatty change and that a true myocarditis was only exceptionally demonstrable. The latter lesion has, however, been recognized by the majority of authors; Holt²² considered toxic myocarditis more important than lesions of the cardiac nerves, especially in the late stage of the disease. Severe and extensive myocardial changes have been described by Councilman, et al.,²³ Price and Mackenzie,²⁴ Aviragnet, et al.,²⁵ and Warthin,²⁶ and Councilman, et al.,²³ stated that these changes were sufficient in themselves to cause cardiac insufficiency. Myocardial lesions have also been observed in experimental animals after injection of diphtheria toxin (Anitschkow,²⁷ Ma, Lieu, and Tung²⁸). Flemming and Kennedy,²⁹ Löw,³⁰ Hume and Clegg,³¹ Farr,³² and Muir³³ described myocarditis involving the bundle of His, and Farr³² even stated that the diphtheria toxin had a specific affinity for this structure. On the other hand, a lesion of the bundle was not regularly found by Aviragnet, et al.,²⁵ in cases in which there had been clinically demonstrable arrhythmias; Tanaka³⁴ found it only rarely in cases of fatal diphtheria; and Rohmer³⁵ stated that the diphtheria toxin showed no affinity for the bundle. Much controversy also exists as to the relative importance and frequency of the parenchymatous and interstitial lesions of the myocardium. Although the majority of authors regard a toxic parenchymatous myocarditis as the primary and important lesion, and the changes in the interstitial tissue as secondary and of a reparative nature, Leyden,⁸ who found diffuse and overwhelming round cell infiltration in the interstitial tissue of the myocardium and only slight fatty change in the muscle fibers, attributed the cardiac failure to an interstitial myocarditis; Birch-Hirschfeld³⁶ even considered the interstitial changes as primary and the parenchymatous

changes as secondary; and Rabot and Philippe³⁷ stated that in their series of observations diphtheritic myocarditis was always of the interstitial type.

In view of the controversial state of the literature regarding the nature and extent of the myocardial lesion, and especially its significance in relation to the cause of cardiac failure, it is desirable to put on record the following case, in which the cardiac failure was adequately accounted for by extensive myocardial necrosis.

CASE REPORT

A Chinese girl, 17 years of age, was admitted with a history of serosanguinous discharge from the nose, severe sore throat, and inability to swallow and to speak for ten days. The onset of the illness was sudden and was followed by light cough. A week prior to admission she developed redness and swelling of the submaxillary region which persisted. There was no subjective feverishness. She had never been immunized against diphtheria.

Examination showed an undernourished, dehydrated, and critically ill patient. The voice was hoarse, but there was no respiratory distress. The skin was free from any kind of eruption. The conjunctivae were slightly congested. The nose was obstructed with serosanguinous discharge and crusts. The lips showed no cyanosis. A dirty necrotic membrane covered the whole throat from the soft palate to the posterior pharyngeal wall. It bled easily. The neck was not rigid. A number of enlarged and tender submaxillary lymph nodes were present on both sides. The lungs were normal. The heart was not enlarged. The heart sounds were normal, and there was no murmur. The cardiac rhythm was regular. The blood pressure was 82/52 mm. Hg. The abdomen was soft, and the liver and spleen were not palpable. The extremities and the reflexes were normal.

Examination of the blood showed 5,030,000 erythrocytes, 17.5 Gm. of hemoglobin, and 39,800 leucocytes, with 86 per cent polymorphonuclear neutrophilic leucocytes. The urine showed 2+ albumin, occasional erythrocytes and leucocytes, and many hyaline and granular casts. The stools were normal but contained ascaris ova. The throat smear showed diphtheria bacilli and spirochetes, but no fusiform bacilli. A culture from the throat swab showed diphtheria bacilli, and also *Streptococcus hemolyticus beta*. *Streptococcus hemolyticus beta*, but no diphtheria bacilli, were cultured from the nose swab. The Schick test was positive.

After admission, 30,000 units of diphtheria antitoxin were given intramuscularly. The dirty membrane in the throat gradually dropped off, leaving behind a raw surface with a big ulcerated area, about 1.5 cm. in diameter, involving the soft palate, pillars, fauces, and a part of the posterior pharyngeal wall. A 3 per cent solution of neocarsphenamine in glycerine was applied locally. The fluid and food intake was so poor that intravenous glucose infusions had to be given daily. Her general condition remained unimproved, and she died rather suddenly, but quietly, twenty-five minutes after the last infusion of 150 c.c. of 10 per cent glucose in normal saline, on the seventeenth day of the disease.

Post-Mortem Observations.—The entire pharyngeal wall was markedly congested and somewhat swollen. On the right lateral pharyngeal wall, and also, to a less extent, on the left pharyngeal wall, irregular, small ulcers, covered with purulent exudate, were found. The right tonsil was slightly enlarged, markedly congested, and superficially but extensively ulcerated. The left tonsil was not enlarged and showed no congestion or ulceration. The lymph nodules at the back of the tongue were very prominent. The submaxillary lymph nodes were swollen, and, on section, appeared juicy. The epiglottis and the arytenoepiglottic folds were edematous.

The mucosa of the larynx showed diffuse swelling and congestion, especially the vocal cords and the ventricular bands. The inner surface of the larynx was covered with a film or fibrinous exudate, mostly on the left, anterior side. The tracheal and bronchial mucosa also showed diffuse swelling and congestion. A film of fibrinous exudate was found over small areas of the trachea in its proximal portion just beneath the larynx, and a small amount of purulent exudate was present in the right bronchus just below the bifurcation of trachea. There was no actual diphtheritic membrane in the pharynx, larynx, or tracheobronchial system. Both lungs showed, on section, a few, small, scattered patches of early lobular consolidation. The tracheobronchial lymph nodes were not enlarged. Cultures taken from the pharynx, larynx, bronchus, and lung showed beta hemolytic streptococci, but no diphtheria bacilli.

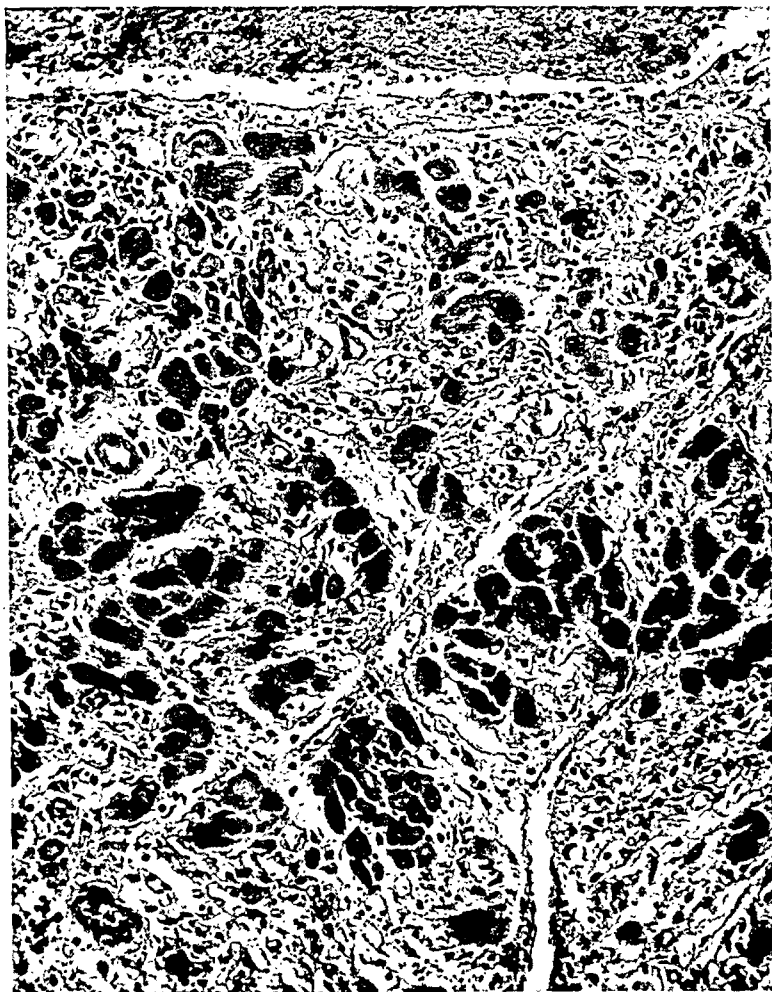


Fig. 1.—Extensive destruction of the myocardial fibers, proliferation of the connective tissue cells, cellular infiltration of the endocardium, and a mural thrombus (at the top of the picture). ($\times 155$.)

The heart was of normal weight (240 Gm.), but showed extreme dilatation of the left ventricle; numerous, fresh, mural thrombi were adherent to the endocardial surface of most of the wall of the left ventricle, and extended between the trabeculae carneae and papillary muscles. The left ventricular surface of the interventricular septum was smooth and free from mural thrombosis. The right auricle and ventricle were also markedly dilated, but showed no thrombi. The left auricle was normal. There were no valvular lesions. The aorta was smooth and elastic.

The liver showed marked central congestion, with a typical nutmeg appearance. The kidneys were markedly congested. Each pleural cavity contained about 1,500 c.c. of clear, straw-colored fluid, and the peritoneal cavity contained about 200 c.c. of similar fluid. Slight edema was present over the ankles and feet.

Grossly, the other organs were not striking.

Microscopically, sections of the larynx stained by the Gram-Weigert method showed numerous Gram-positive cocci in chains in the fibrinous pseudomembrane, but no diphtheria bacilli with Ponder's stain. The Giemsa stain revealed neither fusiform bacilli nor spirochetes in the ulcers of the pharyngeal wall and the tonsil, but numerous Gram-positive cocci in chains were present. Section of the cervical lymph node showed leucocytic infiltration in the marginal and medullary sinuses. Section of the lung showed small scattered patches where the alveoli were distended with leucocytes and fibrin and the bronchioles filled with purulent exudate. The spleen showed no follicular necrosis or leucocytic infiltration of the pulp. The kidneys showed marked degeneration of the convoluted tubules. The suprarenals were normal. The bone marrow of the femur was hyperplastic, with active granulopoiesis.

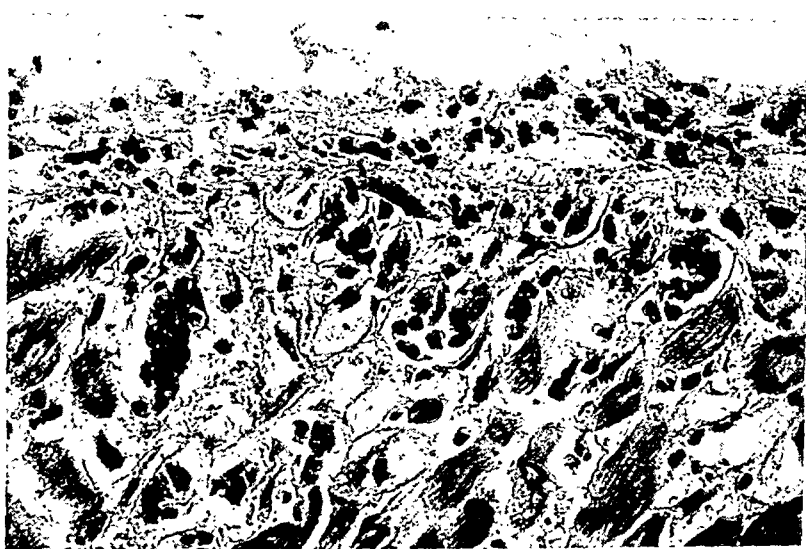


Fig. 2.—Two, necrotic, disintegrating, myocardial fibers (one in the right and the other in the left field of the picture), which are much more deeply stained (with eosin) than the relatively normal fibers, are distinctly granular in appearance and are infiltrated with polymorphonuclear leucocytes. In the middle of the picture, a histocyte can be seen occupying, together with several leucocytes, the space left by the disappearance of a myocardial fiber; above and a little to the left, a connective tissue cell (fibroblast) with a mitotic figure can be seen. In this picture there are many spindle-shaped fibroblasts (cut longitudinally) between the myocardial fibers (which are also cut longitudinally). Note also the leucocytic infiltration of the endocardium. (×295.)

Section of the myocardium showed extensive destruction of the myocardial fibers (Fig. 1), although the sarcolemma sheaths were in most places still preserved (Fig. 3). Inside the sarcolemma sheaths, lumpy or granular acidophilic remains of the myocardial sarcoplasm were frequently found (Fig. 3). In the areas in which the muscle fibers had disappeared, there was proliferation of the connective tissue cells (Figs. 1, 2 and 3). Near the endocardium the lesions were more acute, and fresh necrosis of the myocardial fibers was observed. These necrotic fibers were more deeply stained with eosin than the relatively normal ones; they were distinctly granular in appearance and were infiltrated with polymorphonuclear leucocytes (Fig. 2). Histiocytes were also found among the leucocytes. The endocardium was heavily infiltrated with leucocytes (Fig. 2), and the endocarditis had caused fresh mural thrombosis. The thrombus presented the typical structure of corrugated laminae of platelets, interposed with masses of leucocytes and fibrin. No bacteria

were found in the myocardium or endocardium. Lesions of this nature and of varying degree were found in sections taken from various parts of the left ventricular walls; they were most marked in the apical and lateroposterior portion of the left ventricle, whereas sections from the portions of the interventricular septum in which the bundle of His lay, from the right ventricle, and from the auricles showed no lesions. Thus the extent of the lesions, as ascertained microscopically, corresponded well to the extent of the mural thrombosis which was found grossly. The liver showed marked central congestion and atrophy. The spleen showed marked congestion of the sinusoids. The kidneys also showed marked general injection of the blood capillaries.

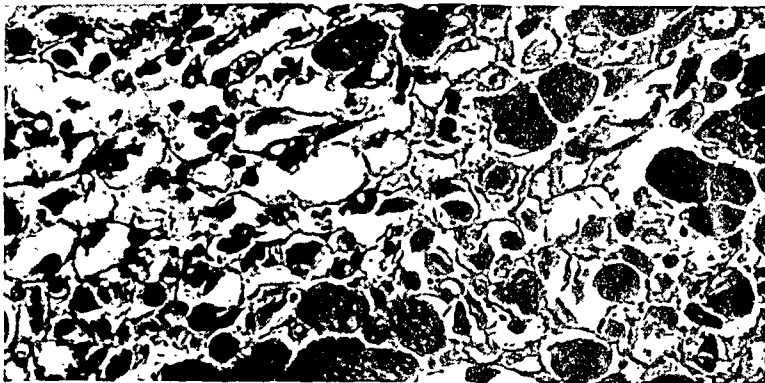


Fig. 3.—Showing disappearance of many myocardial fibers and persistence of the sarcolemma sheaths which describe the outlines of the lost myocardial fibers. Within the sarcolemma sheaths there can be seen irregular, lumpy, or granular, acidophilic remains of the myocardial sarcoplasm. The small cells with dark nuclei are fibroblasts cut transversely (the myocardial fibers in this picture are also cut transversely), and many of these cells are situated inside the sarcolemma sheaths. ($\times 460$.)

Anatomic Diagnosis.—History of pharyngeal diphtheria. Acute ulcerative pharyngitis and tonsillitis, diphtheritic laryngitis, and early lobular pneumonia, bilateral (*Streptococcus hemolyticus beta*); acute cervical lymphadenitis; acute myocardial necrosis, with fresh mural thrombosis of left ventricle; marked dilatation of heart; marked passive congestion of liver, spleen, and kidneys; slight ascites and hydrothorax; edema of ankles and feet; tubular degeneration of kidneys; hyperplasia of bone marrow.

DISCUSSION

There was very little doubt that the patient had a diphtheritic infection of the throat. The points in favor of such an impression were (1) the presence of a dirty necrotic membrane covering the whole throat, (2) the demonstration of diphtheria organisms in both the direct smear and the cultures, (3) the positive Schick test, (4) the response of the local lesion, in the form of disappearance of the membrane, after the injection of diphtheria antitoxin, and (5) the toxic manifestations in the absence of a marked febrile reaction, and the circulatory failure. The ulcerative pharyngitis and tonsillitis were, as shown by the results of culture and of direct staining of the sections, caused by the hemolytic streptococcus which is known to be the most frequent secondary invader in diphtheria infection. The film of fibrinous exudate in the larynx was evidently produced by the streptococcus, which is known to produce such exudates, and was present in the exudate in large numbers. If it

were a residual membrane due to diphtheria infection, Ponder's stain of the section and culture at autopsy should have demonstrated diphtheria bacilli.

The most striking feature of this case was the myocardial necrosis, which was evidently of a toxic nature, since no bacteria were found, and which caused the cardiac failure and fatal outcome. It means that, although the local infection was successfully controlled by antitoxin treatment, the myocardial damage already done by the diphtheria toxin was not affected by it. In the absence of obstruction of the upper respiratory tract and of extensive pneumonia, the marked central congestion and atrophy of the liver indicate that heart failure was present, and this also accounts for the congestion of the spleen and kidneys, the ascites, the hydrothorax, and the edema of the ankles and feet.

With diphtheria infection, myocardial necrosis or parenchymatous myocarditis has been described, although the circulatory failure is not seldom ascribed to vasomotor paralysis because actual myocardial damage is often morphologically not demonstrable. Since it is well known that, in the acute stage of diphtheria, death from circulatory failure is usually due to vasomotor paralysis, but that in the late stage or during convalescence it is usually caused by myocardial damage, lesions of the myocardium were to be expected in this case because the patient died on the seventeenth day of the disease.

However, a review of the literature (quoted in the appendix) reveals that the parenchymatous lesions most frequently found consist of fatty change, hyaline degeneration, and cloudy swelling, whereas true myocardial necrosis is comparatively rare, and that the lesions, except the fatty change, are usually focal and involve only portions of a myocardial fiber. Extensive, diffuse, myocardial necrosis such as was found in our case must, therefore, be considered unusual. The mural thrombosis observed in this case is also of infrequent occurrence, for relatively few authors among those reviewed (D'Espine and Mallet,³⁸ Councilman, et al.,²³ Thomas and Hibbard⁷ and Aviragnet, et al.²⁵) have referred to it. It was evidently secondary to the endocarditis, which, in turn, is secondary to myocardial necrosis, for exactly the same sequence of events occurs in myocardial infarction.

As to whether the extensiveness of the myocardial necrosis in our case was the result of a double infection with the beta streptococcus and diphtheria bacillus one cannot be certain, because, in most cases of diphtheria, there is, at autopsy, secondary streptococcus infection in the upper respiratory tract, and because such extensive myocardial necrosis is even more unusual in toxic streptococcal infections, e.g., scarlet fever.

The majority of authors consider the interstitial changes as a reaction to the parenchymatous lesion, and in our case the inflammatory cellular infiltration and connective tissue cell proliferation were indeed

TABLE I

AUTHOR	MYOCARDIAL LESIONS FOUND
Aviragnet, Lutembacher and Le Soudier ²⁵	Parenchyma: Atrophy, swelling, vacuolation, loss of striation, fragmentation, and a variety of nuclear changes (including karyorrhexis and karyolysis); no fatty change. Changes found throughout myocardium, but especially marked in region of the bundle. Endocarditis and thrombosis purely secondary and incidental. Interstitial tissue: Edema, leucocytes, mononuclears, and proliferation of fibroblasts.
Boyd ⁴²	Parenchyma: Acute toxic degeneration of muscle fibers, with swelling, granular appearance, loss of striations, hyaline degeneration, and necrosis. Only parts of a fiber involved. Interstitial tissue: Secondary inflammation, phagocytic and reparatory in nature.
Bouchut, ⁴³ and Labadie-Lagrave ⁴⁴	Parenchyma: Fatty change frequent; waxy and granular degeneration rare.
Councilman, et al. ²³	Parenchyma: In early stage, fatty degeneration either general or focal, and of varying degree. Then swelling and breaking up into hyaline masses. Vacuolation; fragmentation. No bacteria found. Lesion of toxic nature. Thrombosis not an uncommon condition, and secondary to myocardial necrosis. Interstitial tissue: (1) Focal collections of plasma and lymphoid cells—-independent of myocardial changes. (2) Proliferation of connective tissue cells (secondary to destruction of myocardial fibers. (Some cases of extensive fibrosis, so-called "fibrous myocarditis," of this etiology.)
D'Espine and Mallet ³⁸	Parenchyma: Mural thrombi on auricular and ventricular walls; parenchymatous myocarditis.
Donnerstag ²⁰	Parenchyma: Focal or diffuse fatty change; focal myolysis. Interstitial tissue: Interstitial inflammation sometimes found in late stage of myolysis; connective tissue cell proliferation, with scar formation, seen from beginning of third week of illness.
Farr ³²	Parenchyma: Focal waxy degeneration; focal round cell infiltration of sinoauricular node and bundle of His: widespread myocardial degeneration; fatty change; true myocarditis found once.
Flemming and Kennedy ²⁹	Parenchyma: S-A node and first portion of A-V bundle showed round cell infiltration, congested capillaries, a few large mononuclears, and some polymorphonuclears. Similar changes in auricular and ventricular myocardium.
Guttman ⁴⁵	Parenchyma: Cloudiness or turbidity. Interstitial tissue: Interstitial changes never found.
Hecht ⁴⁶	Parenchyma: Fatty change and cloudy swelling. Interstitial tissue: Round cell infiltration.
Heller ⁴¹	Parenchyma: Granular degeneration commoner than fatty change; waxy degeneration also common, particularly in late stages; simple necrosis of portions of muscle fibers; perimyrial tubes filled with detritus of dead muscle substance, leucocytes, and myogenic cells; evidence of muscle regeneration found. Interstitial tissue: Interstitial reparative reaction.
Hesse ⁴⁷	Parenchyma: Albuminous and fatty degeneration (more marked in early stage). Interstitial tissue: Interstitial myocarditis in late stage (due to changes in blood vessel walls); proliferation of connective tissue cells.
Hochhaus ¹¹	Interstitial tissue: Interstitial myocarditis similar to interstitial myositis of fauces, pharynx, and larynx.

TABLE I—CONT'D

AUTHOR	MYOCARDIAL LESIONS FOUND
Hoyne and Welford ⁴⁸	Parenchyma: Toxic parenchymatous degeneration; scattered hemorrhages in myo- and pericardium.
Huguenin ¹⁰	Interstitial tissue: Connective tissue increased and infiltrated with small round cells. Blood vessels show endarteritis proliferans.
Hume and Clegg ³¹	Parenchyma; Extreme diffuse fatty change. S-A node: congestion, hemorrhage, and lymphocytic infiltration. A-V node and bundle of His: capillary congestion.
Irwin ⁴⁹	Parenchyma: Focal or diffuse fatty degeneration; focal hyaline degeneration, or necrosis. Interstitial tissue: Endocarditis and pericarditis (usually due to streptococci) in less than 2% of cases.
Leyden ⁸	Parenchyma: Slight fatty degeneration. Interstitial tissue: Diffuse and overwhelming round cell infiltration in connective tissue and around blood vessels (cardiac failure in diphtheria due to interstitial inflammation).
Loth ²¹	Parenchyma: Mostly cloudy swelling and fatty change; acute myocarditis and myocardial necrosis exceptional.
Nuzum ³⁹	Interstitial tissue: Eosinophilic infiltration.
Oertel ⁵⁰	Parenchyma: Advanced fatty change in cases of long duration or great severity, with sudden death. Interstitial tissue: Hemorrhage and cellular infiltration.
Oheim ^{51, 52}	Parenchyma: Foci of waxy degeneration, myolysis, fatty change, calcification. Interstitial tissue: Edema; proliferation of connective tissue cells in areas of muscle destruction; perivascular leucocytic and lymphocytic infiltration.
Osler and McCrae ⁵³	Parenchyma: Fatty change in majority of cases; swelling and hyaline degeneration in advanced cases.
Rabot and Philippe ³⁷	Interstitial tissue: Myocarditis always of interstitial type, frequently in the form of focal round cell infiltration.
Romberg ⁵⁴	Parenchyma: Focal fatty, hyaline, and albuminous degeneration; transverse splitting (fragmentation).
Rosenbach ⁵⁵	Parenchyma: Intensive fatty, granular, and waxy degeneration.
Scagliosi ⁵⁶	Parenchyma: More or less diffuse fatty change; loss of striations; hyaline and homogeneous appearance, and intense eosinophilic staining; granular and waxy degeneration; muscle nuclei swollen and increased in number. (Changes only focal, and never involving the entire length of a fiber.) Site of predilection: trabeculae carneae and the zone immediately beneath the endocardium. Interstitial tissue: Marked injection of blood vessels; scattered hemorrhages; round cell infiltration around the degenerated muscle fibers (secondary or reactionary to parenchymatous change, because not found around normal myocardial fibers); blood vessels showed increase number of nuclei in intima, swelling of endothelial cells, hyalinization of media, and slight, small, round cell infiltration of adventitia. Fatty change of vessel wall not found.
Schamschin ⁵⁷	Interstitial tissue: Characteristic picture of interstitial myocarditis; slight fatty degeneration of walls of small arteries; lumen of vessel filled with lymphocytes and phagocytes loaded with fat.
Schemm ⁵⁸	Parenchyma: Fatty change, granular and hyaline degeneration; swelling; multiplication of nuclei.
Tanaka ³⁴	Parenchyma: Fatty change very common; fragmentation occasionally found. Interstitial tissue: Polymorphonuclear, eosinophilic, and mononuclear infiltration.

TABLE I—CONT'D

AUTHOR	MYOCARDIAL LESIONS FOUND
Thomas and Hibbard ⁷	Parenchyma: Small foci showing loss of cross striations, swelling, paling, homogeneous staining (Zenker's degeneration), and vacuolation. Occasionally granular degeneration, atrophy of fibers and fragmentation, focal or extensive fatty change. Many fibers entirely destroyed. Lesion more marked just beneath endocardium; fresh thrombi adherent to myocardium. Interstitial tissue: Edema; infiltration with lymphocytes, large mononuclears, eosinophiles, leucocytes, plasma and epithelioid cells, in varying proportions.
Veronese ⁵	Parenchyma: Degeneration. Interstitial tissue: Round cell infiltration.
Vincent ⁶	Interstitial tissue: Increase of sarcolemma nuclei, capillary hemorrhages, and periarteritis.
Vulfius ⁴⁰	Interstitial tissue: Groups of eosinophiles in connective tissue.
Warthin ²⁶	Parenchyma: Toxic parenchymatous degeneration, most frequently of hyaline nature; necrosis associated frequently with fatty infiltration; cloudy swelling; or a simple necrosis. Muscle regeneration observed. The conducting as well as the contractile tissue may be affected. (Histologic picture depends on duration and stage of disease.) Interstitial tissue: Reparative inflammatory process; fibrosis.

limited to the areas where the myocardial fibers were undergoing necrosis or had disappeared. On the other hand, an independent interstitial inflammation, unassociated with a parenchymatous lesion, can certainly occur in diphtheria as well as in other acute infections (e.g., scarlet fever), and has been reported by many authors quoted in the appendix.

Review of the literature revealed two other points of interest: (1) that an eosinophilic myocarditis has been described by two authors (Nuzum,³⁹ Vulfius),⁴⁰ and (2) that three authors (Warthin,²⁶ Anitschkow,²⁷ Heller⁴¹) claimed to have observed regeneration of the myocardial fibers.

APPENDIX

(Review of the Lesions of the Myocardium in Diphtheria)

The nature, severity, and site of the lesions of the myocardium in diphtheria, as reported in the literature, vary a great deal, and, for comparative study, may be tabulated (Table I).

REFERENCES

1. Romberg, E., Pässler, H., Bruhns, C., and Müller, W.: Untersuchungen über die allgemeine Pathologie und Therapie der Kreislaufstörung bei acuten Infektionskrankheiten. I. Experimentelle Untersuchungen über die allgemeine Pathologie der Kreislaufstörung bei acuten Infektionskrankheiten, Deutsches. Arch. f. klin. Med. 64: 652, 1899.
2. Brodie, T. G.: The Physiological Action of Diphtheria Toxin, Brit. M. J. 2: 128, 1899.
3. Friedmann, U.: Pathogenese der diphterischen Kreislaufschwäche, Deutsches. med. Wehnschr. 58: 1644, 1683, 1932.
4. MacCallum, W. G.: The Mechanism of the Circulatory Failure in Diphtheria, Am. J. Med. Sc. 147: 37, 1914.
5. Veronese, F.: Die postdiphtherische Herzlähmung, eine anatomisch-pathologische und klinische Studie, Wien. klin. Wehnschr. 6: 305, 327, 347, 367, 385, 401, 1893.

6. Vincent, H.: Sur les altérations du plexus cardiaque, dans la paralysie du coeur consécutive à la diphthérie, *Arch. de méd. exper. et d'anat. pathol.* 6: 513, 1894.
7. Thomas, J. J., and Hibbard, C. M.: Heart Failure in Diphtheria, *M. & S. Rep., Boston City Hosp.* 11: 204, 1900.
8. Leyden, E.: Über die Herzaffectationen bei der Diphtherie, *Ztschr. f. klin. Med.* 4: 334, 1882.
9. Unruh: Über Myocarditis bei Diphtherie, *Jahrb. f. Kinderh.* 20: 1, 1883.
10. Huguenin, P.: Contribution à l'étude de la myocardite infectieuse diphthérique, *Rev. de méd.* 8: 790, 995, 1888.
11. Hochhaus: Über diphtherische Lähmungen, *Virchows Arch. f. path. Anat.* 124: 226, 1891.
12. Abramow, S.: Pathologisch-anatomische Studien über experimentelle Diphtherie-Intoxication und Diphtherie-Immunität, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 15: 12, 1912.
13. Nathanson, M. H.: Observations on the Mechanism of Circulatory Failure in Diphtheria, *Proc. Soc. Exper. Biol. & Med.* 24: 398, 1927.
14. Nathanson, M. H.: The Electrocardiogram in Diphtheria, *Arch. Int. Med.* 42: 23, 1928.
15. Begg, N. D.: Diphtheritic Myocarditis, *Lancet* 1: 857, 1937.
16. Thompson, W. P., Golden, S. E., and White, P. D.: The Heart Fifteen to Twenty Years After Severe Diphtheria, *AM. HEART J.* 13: 534, 1937.
17. Perry, C. B.: Persistent Conduction Defects Following Diphtheria, *Brit. Heart J.* 1: 117, 1939.
18. Boyle, R. W., McDonald, C. H., and De Groat, A. F.: The Effect of Diphtheria Toxin Upon the Heart, *AM. HEART J.* 18: 201, 1939.
19. MacCallum, W. G.: Textbook of Pathology, ed. 6, Philadelphia and London, 1936, W. B. Saunders Co., p. 555-56.
20. Donnerstag: Herzveränderungen nach Diphtherie, *Virchows Arch. f. path. Anat.* 287: 421, 1932.
21. Loth, M.: The Heart in Diphtheria, a Clinical and Pathological Study, *Arch. Int. Med.* 31: 637, 1923.
22. Holt, L. E.: Diseases of Infancy and Childhood, New York, 1920, D. Appleton & Co., p. 835-1038.
23. Councilman, W. T., Mallory, F. B., and Pearce, R. M.: A Study of Bacteriology and Pathology of 220 Fatal Cases of Diphtheria, *J. Boston Soc. M. Sc.* 5: 139, 1900.
24. Price and Mackenzie: Auricular Fbrillation and Heart Block, *Heart* 3: 233, 1912.
25. Aviragnet, E. C., Lutembacher, R., and Le Soudier, M.: Le coeur dans la diphthérie, *Arch. d. mal. du coeur.* 11: 241, 1918.
26. Warthin, A. S.: The Myocardial Lesions of Diphtheria, *J. Infect. Dis.* 35: 32, 1924.
27. Anitschkow, N.: Über die Histogenese der Myokardveränderungen bei einigen Intoxikationen, *Virchows. Arch. f. path. Anat.* 211: 193, 1913.
28. Ma, W. S., Lieu, V. T., and Tung, C. L.: Electrocardiographic and Anatomical Changes in Rabbits Poisoned by Diphtheria Toxin, *Chinese M. J. (Supp. 3)*, 574, 1940.
29. Flemming, G. B., and Kennedy, A. M.: A Case of Complete Heart Block in Diphtheria, With an Account of Postmortem Findings, *Heart* 2: 77, 1910.
30. Löw, J.: Beiträge zur Pathologie des Reizleitungssystems, *Ziegler's Beitr.* 99: 1, 1910.
31. Hume, W. E., and Clegg, S. J.: A Clinical and Pathological Study of the Heart in Diphtheria, *Quart. J. Med.* 8: 1, 1914.
32. Farr, C. B.: The Significance of Arrhythmia in Infections of Childhood, With Special Reference to Diphtheria, *Pennsylvania M. J.* 23: 633, 1920 (referred to by Loth).
33. Muir, Sir Robert: Textbook of Pathology, ed. 4, Baltimore, 1936, William Wood & Co., p. 337.
34. Tanaka, T.: Über die Veränderungen der Herzmuskulatur, vor allem des Atrioventrikular-Bündels bei Diphtherie, *Virchows Arch. f. path. Anat.* 207: 115, 1912.
35. Rohmer, P.: Electrocardiographische und anatomische Untersuchungen über den Diphtherie-Herztod und dessen Beziehungen zum Reizleitungssystem, *Ztschr. f. exper. Path. u. Therap.* 11: 426, 1912.
36. Birch-Hirschfeld: *Jahrb. f. d. ges. Natur. u. Heilk.*, 1878-9, p. 26 (referred to by Warthin).

37. Rabot and Philippe: De la myocardite diphthéritique aiguë, Arch. de méd. exper. et d'anat. pathol. 3: 646, 1891.
38. D'Espine and Mallet: Referred to by Loth.
39. Nuzum, F.: Eosinophylous myocarditis in diphtheria, J. A. M. A. 73: 1925, 1919.
40. Vulfius: Vratsh. Gaz., 1914 (referred to by Warthin).
41. Heller, A.: Über die Regeneration des Herzmuskels, Ziegler's Beitr. 57: 223, 1914.
42. Boyd, W.: Textbook of Pathology, ed. 3, Philadelphia, 1938, Lea & Febiger.
43. Bouchut: Gazette des Hôpitaux, 1872, p. 937 (referred to by Scagliosi and Warthin).
44. Labadie-Lagrave: Des complications cardiaques du croup et de la diphthérie, Paris, 1873 (referred to by Scagliosi and Warthin).
45. Guttman, P.: Referred to by Scagliosi and Warthin.
46. Hecht, A. F.: Der Mechanismus der Herzaktion im Kindesalter, seine Physiologie und Pathologie, Ergebn. d. inn. Med. u. Kinderh. 2: 324, 413, 1913.
47. Hesse, B.: Beiträge zur pathologische Anatomie des Diphtherieherzens, Jahrb. f. Kinderh. 36: 19, 1894.
48. Hoyne, A., and Welford, N. T.: Diphtheria Myocarditis; Review of 496 Cases, J. Pediat. 5: 642, 1934.
49. Irwin, R. L.: Essential Pathology Found in Diphtheria, Scarlet Fever, and Tuberculosis, With Special Reference to Involvement of Heart Based on Review of Necropsy Cases at Boston City Hospital for Past 40 Years, New England J. Med. 207: 863, 1932.
50. Oertel: Experimentelle Untersuchungen über Diphtherie, Deutsches. Arch. f. klin. Med. 8: 242, 1871.
51. Oheim, L.: Herzmuskelveränderungen bei Diphtherie, ihre zeitliche Aufeinanderfolge und topographische Verteilung, Ziegler's Beitr. 100: 195, 1938.
52. Oheim, L.: Herzmuskelverkalkung bei Diphtherie, Ziegler's Beitr. 100: 222, 1938.
53. Osler, W., and McCrae, T.: Principles and Practice of Medicine, New York and London, 1920, Appleton & Co.
54. Romberg, E.: Über die Erkrankungen des Herzmuskels bei Typhus abdominalis, Scharlach und Diphtherie, Deutsches. Arch. f. klin. Med. 48: 369, 1891.
55. Rosenbach, J.: Über Myocarditis diphtheritica, Virchows Arch. f. path. Anat. 70: 352, 1877.
56. Scagliosi, G.: Über die Veränderungen des Herzmuskels bei Diphtherie. Virchows Arch. f. path. Anat. 146: 115, 1896.
57. Schamschin, W.: Beiträge zur Pathologie des Herzmuskels, Ziegler's Beitr. 18: 47, 1895.
58. Schemm, G. C.: Über die Veränderungen des Herzmuskulatur bei Rachendiphtherie, Virchows Arch. f. path. Anat. 121: 235, 1890.

Department of Clinical Reports

TUBERCULOUS PERIPHERAL ARTERITIS ASSOCIATED WITH TUBERCULOUS THROMBOPHLEBITIS IN THE LUNGS

WILLIAM NEEL, M.D., AND LOUIS G. HERRMANN, M.D.
CINCINNATI, OHIO

TUBERCULOUS arteritis of large peripheral arteries has been observed infrequently, whereas tuberculosis of the pulmonary vessels is probably present in every case of pulmonary tuberculosis. Search of the literature discloses, however, that tuberculous thrombophlebitis of the pulmonary vessels of such magnitude as to give rise to large emboli and metastatic foci of tuberculous arteritis in the large arteries of the periphery is sufficiently rare to justify recording this case.

The relationship between tuberculosis involving the vascular system and its generalized miliary dissemination was noted by Weigert,¹ in 1877. In the process of tuberculous cavitation, the vessels lying in the walls are encroached upon by the granulation tissue. As the adventitia and media are replaced by granulation tissue, the intima become thickened. When the walls of the cavity and artery have fused, the vessel may bulge, giving rise to the aneurysm of Rasmussen. Occasionally, rupture leads to severe hemoptysis; this, however, is usually prevented by intravascular thrombosis. Generalized miliary tuberculosis frequently results when a caseous process in a hilar lymph node erodes into the lumen of a pulmonary vein and discharges its infected contents into the blood stream.

In 1913, Haythorn² reported a case of tuberculous aneurysm involving the right common iliac artery. The patient was a man, aged 33 years. The clinical diagnosis was generalized miliary tuberculosis, chronic pulmonary and right-sided renal tuberculosis, tuberculous enteritis, and aortic aneurysm. At necropsy an aneurysm of the right common iliac artery was found; this aneurysm measured 7 cm. in breadth and 3 cm. in thickness. Its wall appeared to be continuous with the common iliac artery above, and with the internal iliac artery below. When the vessels were opened, the aneurysm was found to involve only the common iliac artery. The interior of the sac was almost filled with reddish-gray thrombotic material which appeared caseous. Histologic study showed

From the Department of Pathology of the University of Cincinnati College of Medicine and the Vascular Disease Service of the Department of Surgery of the Cincinnati General Hospital.

Received for publication July 1, 1940.

that the outer wall of the sac was continuous with the adventitia of the common iliac artery below. Great numbers of acid-fast bacilli were demonstrated in the wall of the aneurysm, and in miliary lesions in the kidney, lungs, spleen, and liver. Haythorn² believed that the tuberculous process in this case originated in some adjacent focus, and the direct invasion of the adventitia so weakened the circular muscle fibers of the media that they ruptured. The continued pressure of the blood pouring through the opening divided the inner layers of the media from the outer medial layers and adventitia, resulting in a dissecting aneurysm. When the blood in the sac clotted, it became infected by the process in the adventitia. From this focus tubercle bacilli were disseminated throughout the blood stream. Haythorn² also classified the various kinds of tuberculous arterial lesions. He described them under four general types: (1) Miliary tuberculosis of the intima, (2) polypi of tuberculous tissue attached to the intima, (3) tuberculosis of the wall, involving all the layers, and (4) aneurysms, the walls of which were composed of tuberculous tissue.

In 1928, Malcolm³ reported an aneurysm caused by tuberculosis in a man, aged 72 years. The patient had a right-sided, indirect, inguinal hernia for which he had worn a truss for many years. He died twenty-four days after a painful swelling appeared suddenly in the right thigh below Poupart's ligament. Autopsy disclosed generalized miliary tuberculosis, with a ruptured right femoral aneurysm caused by tuberculous arteritis. Hemorrhage was present about the right femoral artery. There was thrombosis of the femoral vein and its tributaries, as well as of the right femoral artery below the aneurysm. Microscopic examination revealed engorgement of the vessels of the adventitia. Extensive necrosis was present in all coats, with slight fibrous connective tissue proliferation. Giant cells were observed, but their character and location were not described. The acid-fast bacilli demonstrated in the media conformed to the size, shape, and staining reactions of the tubercle bacillus.

Brenner,⁴ in 1935, indicated that tuberculous granulation tissue may extend along the lumen of a vessel for some distance before the wall becomes invaded. The extension of the thrombophlebitis to a large intrapulmonary vein results in a thrombus which is of sufficient size to give rise to embolism in peripheral arteries.

In 1939, Thieme and Maddock⁵ described a case of "primary, tuberculous, peripheral vascular disease" in which no adjacent or other tuberculous processes were found, and no tubercle bacilli demonstrated.

At least twenty cases of tuberculosis of peripheral arteries, associated with aneurysm, have been reported. In five of these cases neighboring tuberculous processes were described. For instance, Thompson⁶ reported related tuberculous lymph nodes. Brockman⁷ and Ribbert⁸ found the diseased artery in an area of tuberculous spondylitis.

The process of tuberculous aneurysm formation was described by Eppinger⁹ as starting from embolic occlusion of one of the vasa vasorum, with resulting peri- and mesarteritis. When the elastica and adventitia are destroyed, the weakened vessel wall sacculates. Malcolm,³ who found organisms only in the media, believed that his case was one of the kind described by Eppinger.⁹ Le Noble¹⁰ reported tuberculous nodules on the mitral valve, associated with peripheral arteritis and aneurysm.

CASE REPORT

A white woman, aged 21 years, was admitted to Cincinnati General Hospital on Sept. 13, 1939, because of marked dysphagia. The patient was in her sixth month of pregnancy. She had enjoyed good health until three months before admission, when she noticed the gradual onset of a moderately painful sore throat, followed by persistent hoarseness. The flow of saliva increased, and she frequently had nausea and vomiting. The act of swallowing became extremely painful, and frequently resulted in regurgitation of fluids into the nasopharynx.

There was no history of contact with tuberculosis. In 1937 and 1938 the patient had had attacks of transitory, severe, sore throat.

On physical examination the temperature by mouth was 103.4° F., the pulse rate, 128 per minute; the respiratory rate, 24 per minute; and the blood pressure, 100/60. The pale, poorly nourished patient had a roughened voice. She apparently preferred to allow profuse, thin, watery saliva to drool from the mouth rather than experience the pain of swallowing. The moderately swollen, red tonsils were covered with grayish-white membranes. An irregularly outlined area of ulceration extended from the tonsils over the anterior pillars and soft palate. The pale red, granular, ulcer bases were covered with patchy grayish-white exudate. The true and false vocal cords were somewhat swollen. The large, firm breasts presented pigmentation of the areolae and contained colostrum. The symmetrical chest expanded only moderately on respiration. The right middle lobe and both upper lobes of the lungs were normal to percussion and auscultation. The lower lobes were consolidated. The abdomen was enlarged by the gravid uterus, which extended above the umbilicus.

Throat cultures revealed the presence of hemolytic streptococci, colonies of *Staphylococcus aureus*, and many Gram-positive bacilli. The erythrocyte count was 3,460,000 per cubic millimeter. The leucocyte count was 7,800 per cubic millimeter, and remained low.

The condition of the patient became progressively worse, with elevation of the temperature, increasing dyspnea, cyanosis, and profuse sweating.

A 8:00 A.M. on the tenth hospital day there was a sudden onset of persistent, severe pain in the left foot. The foot promptly became cold. The patient soon complained of numbness and tingling in this foot. Reddish-blue, livid mottling appeared on the dorsum of the third and fourth toes. The coldness extended from the foot to midcalf. No pulsation could be felt in the dorsalis pedis, posterior tibial, popliteal, and femoral arteries of the left leg. All of the normal pulses were present in the warm right leg. The diagnosis of acute embolic occlusion of the left femoral artery was made, and passive vascular exercise was started seventeen hours after the recognized onset of acute arterial occlusion. The method consisted of applying, alternately, a positive pressure of 60 mm. of mercury and a negative pressure of 20 mm. of mercury twice a minute. The slow, rhythmic cycle was intended to overcome the intense arterial spasm set up by the arterial occlusion. As is usual when the patient is acutely ill, this treatment was somewhat tiresome.

Therefore, after two hours of treatment the foot was removed from the warm boot, wrapped in blankets, and allowed to rest for one hour. However, the respiratory rate rose to 68 per minute; cyanosis increased; and profuse sweating and a fall in blood pressure to 70/40 appeared. Meanwhile, the reddish-blue mottling of the foot had extended to the ankle. After twenty-six hours, passive vascular exercise was discontinued because of the critical condition of the patient and the progress of the arterial thrombosis in the proximal portion of the injured artery.

The patient died on the sixteenth hospital day, and an immediate cesarean section was done. An apparently normal, premature, male infant was delivered, but died fourteen days later of lobular pneumonia. Careful post-mortem examination of the infant did not reveal evidence of tuberculosis.

Necropsy on the mother showed generalized tuberculosis involving the lungs, liver, spleen, kidneys, suprarenals, intestine, breasts, placenta, tonsils, epiglottis, and vocal cords. Thromboarteritis and thrombophlebitis of the lungs were associated with recent pulmonary infarction and embolic occlusion of the external iliac artery.

The external iliac artery was distended throughout its entire extent, and its lumen was completely occluded by an adherent thrombus. The adventitia was dark blue, with irregularly mottled red areas. The clot in the lumen of the artery, in its most proximal and distal portion, had the character of a secondary red thrombus. The middle portion of the thrombus was white and firmly adherent.

Cross sections of the vessel were made at various levels; these were studied microscopically. In relation to the red thrombus, the vessel wall showed little evidence of disease. However, sections through the white thrombus disclosed a definitely laminated clot, with areas of caseous necrosis, associated with acute inflammatory changes throughout the arterial wall. The endothelium was completely destroyed. The intima was densely infiltrated with polymorphonuclear leucocytes and lymphocytes, many of which had undergone karyorrhexis and pyknosis. This process was often limited by the internal elastic lamella, but this was frequently fragmented by areas of caseous necrosis which extended into the media. Evident in the slightly congested adventitia were an extensive proliferative reaction of connective tissue and vascular endothelium and an infiltration of inflammatory cells, predominantly those belonging to the lymphoid and endothelial series. In occasional areas, however, the polymorphonuclear leucocytes were prominent. No foreign-body giant cells were observed in any of the sections of the artery. A small adjacent lymph node showed only rarefaction of the germinal centers, with proliferation of the reticulum. Acid-fast bacilli, which, in size, shape, and staining reactions, had the characteristics of tubercle bacilli, were demonstrated in the white thrombus, media, and adventitia, as well as in the generalized nodular lesions. No microorganisms were found in the nearby lymph node.

SUMMARY

Tuberculous arteritis of large peripheral arteries is frequently associated with aneurysm. In two of the twenty reported cases acid-fast bacilli were demonstrated.

A case of tuberculous arteritis as the result of embolism from tuberculous thrombophlebitis of pulmonary veins is reported. No aneurysm was present. The lumen of the artery was filled with a caseous white thrombus, and there were areas of inflammation and caseous necrosis in the intima and media and proliferation of connective tissue and vascular endothelium, with infiltration of lymphocytes and epithelioid

cells in the adventitia. No foreign-body giant cells were seen. Tubercle bacilli were demonstrated in the white thrombus, in the arterial wall, and in the lesions of generalized miliary tuberculosis.

REFERENCES

1. Weigert, C.: Ueber Venentuberkel und ihre Beziehungen zur tuberkulösen Blutinfektion, *Virchows Arch. f. path. Anat.* 88: 308, 1882.
2. Haythorn, S. R.: Tuberculous Aneurysm, Involving the Right Common Iliac Artery, *J. A. M. A.* 60: 1414, 1913.
3. Malcolm, R. B.: Aneurysm Due to Tuberculosis With the Report of a Case of Tuberculous Aneurysm of the Right Femoral Artery, *Canad. M. A. J.* 19: 33, 1928.
4. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation, *Arch. Int. Med.* 56: 1189, 1935.
5. Thieme, T., and Maddock, W. G.: Primary Tuberculous, Peripheral Vascular Disease, *Surgery* 6: 604, 1939.
6. Thompson, W. P.: Tuberculous Aneurysm of Hepatic Artery, *Bull. Johns Hopkins Hosp.* 42: 113, 1928.
7. Brockman, E. P.: Aneurysm of the Femoral Artery in a Patient With Pott's Disease of the Spine, *Brit. J. Surg.* 14: 669, 1927.
8. Ribbert: Mitteilung über ein tuberkuloses Aneurysma der Aorta, *Sitzungsb. d. Nied-rhein, Gesellsch. f. Nat. und Heilk.* 24 Bonn, med. section, May 14, 1910.
9. Eppinger: Pathogenesis (Histogenesis and Aetiologie) der Aneurysmen, *Arch. f. klin. Chir.* 35: Suppl. 156, 1887.
10. Le Noble, Pel.: Aneurisme de la portion initiale de l'aorte, *Arch. d. mal. du coeur* 15: 677, 1922.

CORONARY ARTERY THROMBOSIS, WITH RECOVERY, IN A CASE OF THROMBOANGIITIS OBLITERANS

IRVING GREENFIELD, M.D.
BROOKLYN, N. Y.

IN 1879, von Winiwater¹ reported occlusion of the arteries of both lower extremities by a chronic proliferative process arising from the intima of the vessels. Microscopic sections of these vessels showed an inflammatory reaction in their walls. This lesion was called endarteritis obliterans. Thereafter, occasional reports appeared describing similar pathologic processes. Buerger² called attention to the thrombotic and inflammatory nature of the process, the involvement of veins as well as arteries, and the characteristic clinical phenomena of the disease which now bears his name. From a review of the literature, one is impressed with the fact that thromboangiitis obliterans is not a rare disease. Aver-buck and Silbert³ and Cohen and Barron⁴ have noted that thromboangiitis obliterans is not restricted to the vessels of the extremities. The literature is rich in clinical, pathologic, and experimental data dealing with the various types of coronary artery thromboses. However, there is a paucity of reports concerning the occurrence of coronary thrombosis in cases of thromboangiitis obliterans.

CASE REPORT

A. S., a 40-year-old man, was first seen in September, 1935, when he was complaining of pain in the left large toe of one year's duration. During the preceding winter he noticed that he was much more sensitive to cold than he had been previously, and for eight months he had had an ulcer on the left large toe which did not respond to a variety of self-prescribed ointments. He slept poorly because of the burning pain. The patient admitted smoking thirty to forty cigarettes daily, and, for many years, he had eaten four to five slices of rye bread daily. The remainder of his history was noncontributory except for the fact that he had had gonorrhea when he was 19 years of age.

The blood pressure was 124/80. At the tip of the left large toe there was an open ulcer which measured 0.5 by 0.25 inch and had undermined edges and a necrotic base. The extremities were cold to the touch below the level of the lower one-third of the leg. There was moderate cyanosis of both lower extremities on dependency, with a cyanotic rubor of the left large toe. There was marked pallor on elevation. The dorsalis pedis and posterior tibial pulsations were absent. The pulsation of the popliteal vessels was easily palpated. The maximum oscillometric readings at the levels indicated are given in Table I. Roentgenologic examination of the lower extremities showed no evidence of calcification of the vessel walls.

Received for publication July 1, 1940.

The patient was advised to stop smoking cigarettes and eating rye bread, was instructed concerning exercises and hygiene of his extremities, and was given two intravenous injections of typhoid vaccine. He had a rather severe reaction after each injection and refused to return for further therapy.

TABLE I
MAXIMUM OSCILLOMETRIC READINGS

LEVEL	RIGHT	LEFT
Thigh	4.5	5.0
Leg	3.0	3.0
Ankle	0.5	0.25
Foot	0	0

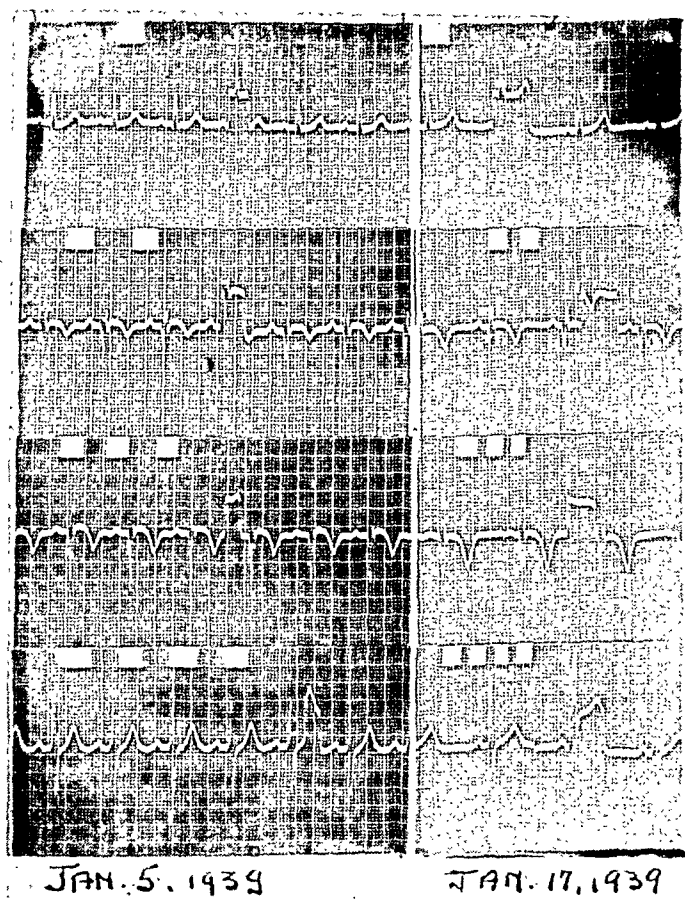


Fig. 1.—Electrocardiograms taken Jan. 5, 1939, and Jan. 17, 1939, showing elevation of R-T₂ and R-T₃, with inversion of T₂ and T₃. Lead IVF shows no change except that S₄ in the second electrocardiogram is not so deep as in the first.

The patient was not seen again until March, 1938, when he returned with an open ulcer on the plantar surface of the right foot; the ulcer had been present for three weeks. The interval history revealed the fact that the ulcer on the left large toe had healed, and the patient had been able to walk about ten blocks without discomfort. He stated that he felt so well that he had even begun to smoke cigarettes again. After he started to smoke, his claudication distance gradually grew shorter and shorter, so that, on his second admission, he was able to walk only one-half block before pain forced him to stop. At this time he had marked rubor on dependency, trophic changes in all of the toenails, and cadaveric pallor on elevation. There was an ulcer measuring about $\frac{1}{2}$ by $\frac{3}{4}$ inch on the plantar surface of the right foot at

the head of the third metatarsal bone. Oscillometric studies revealed essentially the same readings as on the first examination. He received a course of typhoid H antigen injections. The ulcer healed in three months. While he was under observation, the patient did not smoke.

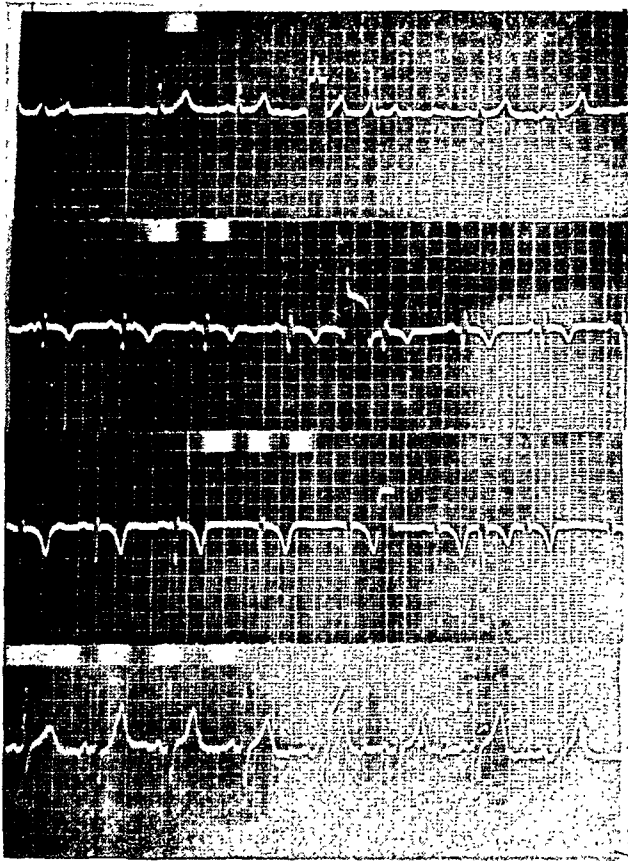


Fig. 2.—Electrocardiogram taken Jan. 30, 1939, showing ventricular premature contractions in Lead III.

The patient was not seen again until Jan. 2, 1939, when, after exertion incident to lifting and adjusting snowplows to trucks, he was seized with sudden, severe, precordial pain which radiated to the neck and jaw and down both arms. He complained of feeling nauseated, but he did not vomit. He rested for about one-half hour, and then completed his day's work. He went home and remained in bed for forty-eight hours. The pains were thought to be gas pains. He then returned to work and shoveled coal into a furnace. While doing this he was seized again with precordial distress which was more severe. He was nauseated but did not vomit. He began to perspire freely and felt weak. He had a fear of impending dissolution. He went home and was examined immediately. His expression was a mixture of fear and anxiety. He had circumoral pallor; his lips were cyanotic; and his respirations were rapid. His blood pressure was 90/70, and his temperature, 99.2° F. The heart tones were heard with difficulty. There was no friction rub. The pulse rate was 120 per minute. The edge of the liver was palpable 1.5 fingerbreadths below the costal margin; it was soft and tender. The spleen was not enlarged. No pulsation could be felt in the major vessels of the lower extremities. The nail beds were cyanotic. An electrocardiogram taken Jan. 6, 1940, revealed the T_2T_3 type (Fig. 1) of changes which are typical of posterior wall infarction. The sedimentation rate

was rapid (17 mm. in one hour). The leucocyte count was 11,000, 78 per cent of which were polymorphonuclears, and his temperature rose to 101° F. His precordial distress subsided, and the temperature, sedimentation rate, and leucocyte count returned to normal. About twenty-seven days after the occlusion the pulse became somewhat irregular; this irregularity was caused by frequent ventricular premature contractions, as shown by an electrocardiogram (Fig. 2).

The patient made an uneventful recovery. A follow-up examination (June, 1940) revealed no further advance in the vascular process, either in the extremities or in the coronary vessels. He has given up smoking completely, and he is able to work eight hours daily at laborious tasks.

The protocol of a 44-year-old man who died from thromboangiitis obliterans of the left common iliac artery, with extension into the aorta as far as the left renal artery, was recorded by Perla.⁵ An organized, canalized thrombus almost completely occluding the lumen of the left coronary artery 1.5 cm. from its aortic orifice was found. The pathologic process in this coronary artery resembled that in the diseased vessels of the extremities. Barron and Linenthal⁶ observed coronary thrombosis in one of twenty-seven cases of thromboangiitis obliterans which they collected. These authors noted that the disease involves the walls of arteries, as well as veins, throughout the entire vascular system. Myocardial damage which Samuels and Feinberg⁷ attributed to involvement of the coronary arteries by thromboangiitis obliterans was noted in five of their fifty cases. Allen and Willius⁸ observed clinical evidence of disease of the coronary arteries in seven of a series of 225 unselected cases of thromboangiitis obliterans. Six patients had definite electrocardiographic evidence of involvement of the coronary arteries. The remaining electrocardiogram was normal, in spite of the fact that the patient was a 47-year-old man who complained of choking sensations, severe pain across the anterior, lower part of the chest and down both arms, and dyspnea on exertion.

Fatherree and Hines⁹ reviewed forty cases from the literature. The diagnostic criteria for thromboangiitis obliterans were adequate and the cause of death was established by necropsy. In three of the nine cases in which death occurred after operation, and, in twenty-three in which death did not follow operation, occlusive arterial disease in locations other than the extremities played a dominant role as a cause of death. Ten of the twenty-three nonpostoperative deaths were caused by coronary thrombosis. An analysis of the data led these authors to the conclusion that by far the most common extraperipheral cause of death in cases of Buerger's disease is coronary thrombosis. However, Allen and Willius⁸ observed that the incidence of coronary artery disease in cases of known thromboangiitis obliterans was no greater than in a control group.

A prolonged discussion of Buerger's disease or coronary artery thrombosis is not necessary here. Speculation as to the relationship of the

attack of coronary artery occlusion to the present conception of the universal nature of the vascular involvement in Buerger's disease is of interest. The occurrence of coronary artery thrombosis after unusual effort has been discussed by Boas.¹⁰ The idea that thromboangiitis obliterans is a generalized vascular disease, rather than a disease involving only the vessels of the lower extremities, has been accepted.

SUMMARY

A case of coronary artery thrombosis, with recovery, in a 40-year-old man with known thromboangiitis obliterans is reported.

REFERENCES

1. Von Winiwater, F.: Über eine eigentümliche form von Endarteritis und Endophlebitis mit Gangrän des Fusses, *Arch. f. klin. Chir.* 23: 202, 1879.
2. Buerger, L.: Thromboangiitis Obliterans. A Study of the Vascular Lesions Leading to Presenile Spontaneous Gangrene, *Am. J. M. Sc.* 13: 567, 1908.
3. Averbuck, S. H., and Silbert, S.: Thromboangiitis Obliterans. IX. The Cause of Death, *Arch. Int. Med.* 54: 436, 1934.
4. Cohen, S. S., and Barron, M. E.: Thromboangiitis Obliterans With Special Reference to Its Abdominal Manifestations, *New England J. Med.* 214: 1275, 1936.
5. Perla, D.: An Analysis of 41 Cases of Thromboangiitis Obliterans, *Surg, Gynec. & Obst.* 41: 21, 1925.
6. Barron, M. E., and Linenthal, H.: Thromboangiitis Obliterans, General Distribution of the Disease, *Arch. Surg.* 19: 735, 1929.
7. Samuels, S. S., and Feinberg, S. C.: The Heart in Thromboangiitis Obliterans, *AM. HEART J.* 6: 255, 1930.
8. Allen, E. V., and Willius, F. A.: Disease of the Coronary Arteries Associated With Thromboangiitis Obliterans of the Extremities, *Ann. Int. Med.* 3: 35, 1929.
9. Fatherree, T. J., and Hines, E. A.: Vascular Clinics. IV. Fatal Complications of Thromboangiitis Obliterans. A Clinical Study, *Proc. Staff Meet., Mayo Clin.* 13: 842, 1938.
10. Boas, E.: Angina Pectoris and Cardiac Infarction From Trauma or Unusual Effort, *J. A. M. A.* 112: 1887, 1939.

Department of Reviews and Abstracts

Selected Abstracts

Katz, L. N., Jochim, K., Lindner, E., and Landowne, M.: The Effect of Varying Resistance-Load and Input-Load on the Energetics of the Surviving Mammalian Heart. *Am. J. Physiol.* 134: 636, 1941.

A method is described for obtaining a true mixed coronary venous blood sample in the heart-lung or isolated heart preparation of the dog, and for calculating the true oxygen consumption of the heart.

Measurements of oxygen consumption and work of the heart preparation indicate that the increase in oxygen consumption consequent upon an increase in work depends not only upon the magnitude of the work increase, but also on whether the augmented work is produced by raising (1) the venous return or (2) the peripheral resistance. In the former case the increase in oxygen consumption is proportionally less than in the latter, so that a given amount of work is done more efficiently with a large venous return and a low peripheral resistance than the same amount of work done with a low venous return and a high peripheral resistance.

AUTHORS.

Weltz, G. A.: Effect of Respiration on Filling and Rate of Heart. *Arch. f. Kreislaufforsch.* 8: 1, 1941.

By means of roentgenkymography, electrocardiograms, pneumotachygrams and plethysmography of the limb on human and on animal subjects, an investigation of effects of respiration were made. It was found that there is a respiratory fluctuation in the venous return to the heart, which normally consisted of an increase in inspiration. This is associated with a reflex pulse acceleration. Under certain abnormal circumstances, such as artificial respiration, the inspiratory increase in venous flow to the heart is decreased and with it there is a cardiac slowing instead of an acceleration in inspiration.

KATZ.

Starr, I.: Clinical Studies With the Ballistocardiograph: In Congestive Failure, on Digitalis Action, on Changes in Ballistic Form, and in Certain Acute Experiments. *Am. J. M. Sc.* 202: 469, 1941.

This presentation is designed to demonstrate the utility of the ballistocardiogram as an instrument of the diagnosis of cardiac and circulatory abnormality and for the solution of certain clinical problems. Records are presented indicating changes in the circulation in congestive heart failure and on recovery from it, during digitalis action, and in various arrhythmias in one patient.

The method is suited especially for acute clinical experiments. The examples cited include ballistocardiograms from a case of traumatic arteriovenous communication before and during occlusion of the communication and similar records from a patient

with angina pectoris in whom pain was produced by the injection of fluid down a drainage tube into the common bile duct.

Changes in the form of the ballistic record provide evidence of cardiac dysfunction of a type not obtainable by other methods. The examples cited were obtained from three patients in whom the abnormality followed operative procedures and disappeared as strength was regained.

AUTHOR.

Baer, S., and Isard, H. J.: A Correlation of the Velocity of Blood Flow and the Basal Metabolic Rate in Various Metabolic Disorders. Arch. Int. Med. 67: 939, 1941.

An attempt has been made to determine what correlation, if any, existed between the basal metabolic rate and the velocity of blood flow. Basal metabolic rates and circulation times were determined in 187 patients. After the injection of 4 c.c. of a 20 per cent solution of calcium gluconate intravenously, the circulation time was measured from the instant the injection was begun until the patient noticed a sensation of heat in the oropharynx.

In 227 trials, the normal arm-to-tongue time varied from nine to sixteen seconds, with an average of 12.1 seconds. In twenty-four patients with hyperthyroidism, the average circulation time was 8.9 seconds, and in hypothyroidism the circulation time was usually prolonged beyond sixteen seconds. Thus, the velocity of blood flow is increased in hyperthyroidism and decreased in hypothyroidism.

In cases of polyglandular dystrophy however, or those patients with menopausal syndromes and hypertension, the calcium gluconate circulation time bears no relation whatsoever to the B.M.R. In children, irrespective of the basal metabolic rate, the velocity of blood flow is increased.

The authors feel that the determination of the velocity of blood flow may be of some help in the diagnosis of thyroid gland disturbances. A basal metabolic rate of plus 20 or above and an arm-to-tongue circulation time of ten seconds or below are strongly suggestive of active hyperthyroidism.

AUTHOR.

Moe, Gordon K., Harris, A. S., and Wiggers, C. J.: Analysis of the Initiation of Fibrillation by Electrographic Studies. Am. J. Physiol. 143: 473, 1941.

The mechanism by which ventricular fibrillation develops as a result of a strong, brief D. C. shock delivered during the vulnerable period of the ventricular cycle was studied electrographically. Three pairs of contiguous electrodes operating on the principle of Garten differential electrodes were variously oriented on the ventricular surface with respect to the site of stimulation in different tests on the same heart. Since the ventricles were repeatedly revived by the countershock method of Hooker, the ventricular surface was sampled reasonably well by changing the placement of electrodes.

The following results and conclusions are discussed.

A moderately strong, brief shock applied considerably before the T wave of an electrogram recorded at, or near, the point of stimulation causes one response shortly after the T wave. Tests are presented which indicate that the response is probably not due to an actual systolic excitation but to the creation in tissue of a decrementing polarization potential which is sufficient in duration and intensity to excite early in the next relatively refractory phase. In this way the response of the ventricle to a systolic shock can be harmonized with the existence of a refractory state in muscle fractions. It also explains why the latency of responses at definite points on the cardiac surface remains constant for shocks applied at any moment of diastole, but

increases linearly as they are applied more and more in advance of the T wave of a local electrogram. No evidence has been found in the dog's heart that changes in conduction are involved in such increasing latency; the interpunctal differences between excitation lines remain the same, regardless of when the stimulus is introduced.

A very strong shock applied to a discrete mass of ventricular muscle during the Q-T interval of an adjacent electrogram evokes a series of deflections in all electrograms led from the cardiac surface. This may be followed by a pause and resumption of normal rhythm or by fibrillation. When the latter occurs, it develops in the nearest surface lead slightly before it does in the others.

The series of discrete deflections recur at progressively decreasing intervals in the most proximal lead, and the excitation times more distant in relation to proximal points increase progressively during the series of responses.

The order of excitation on the surface and interior of the ventricle during the second, third, and fourth responses and the existence of a period between beats when no area is excited do not support the view that the initial beats are due to re-entry of impulses. On the contrary, the concentric arrangement of isochrons calculated from actual records strongly suggests repetitive emission of several impulses from the stimulated area, temporarily made automatic by the shock.

Deflections similar in form and sequence in near and far areas of the heart could be caused artificially by applying a series of weak threshold break induction shocks at slightly diminishing intervals. If given in proper sequence, these also cause fibrillation.

The conclusion is drawn that the re-entry of impulses, with which fibrillation following localized application of a strong, brief D. C. shock starts, is due to the progressive decrease in refractory period combined with a progressive increase in conduction time. This starts in regions near the site of stimulation and occurs as a result of the repetitive accelerating discharges rather than as an effect of the current per se. In short, while repetitive discharges from a center or centers are not required to sustain fibrillation, they are essential to its initiation after a strong electrical shock.

AUTHORS.

Wiggers, C. J.: *The Mechanisms of Peripheral Circulatory Failure.* Ann. Int. Med. 15: 178, 1941,

In this brief discussion the author reviews the fundamental factors involved in peripheral circulatory failure. He discusses the four mechanisms which have been suggested and can be supported by experimental evidence. They are (1) primary arteriolar dilatation, (2) primary arteriolar constriction, (3) primary atony and dilatation of capillaries and (4) primary failure of some venopressor mechanism.

It is obvious that this problem is still worthy of investigation and that the answer has not yet been found to the many questions involved.

McCULLOCH.

Fouts, P. J., Corcoran, A. C., and Page, I. H.: *Observations on the Clinical and Functional Course of Nephrotoxic Nephritis in Dogs.* Am. J. M. Sc. 201: 313, 1941.

Nephrotoxic nephritis due to injection of relative organ-specific nephrotoxic sera in dogs is at its onset associated with increased renal blood flow and decreased efficiency of glomerular filtration.

The decrease of glomerular efficiency is apparently due to thickening of the glomerular basement membrane. This functional alteration persists during the course

of active nephritis. Its presence is indicated by an increase in the ratio of phenol red to inulin clearance.

The hematuria which is observed at the onset of nephrotoxic nephritis in the dog and during the persistence of severe chronic nephritis is apparently not related to hemolytic or anaphylactic reactions which may follow the injection of sera.

Although the acute anemia which followed injection of nephrotoxic sera in dogs is due to hemolytic factors present in the sera, the course of the anemia subsequent to the development of nephritis suggests that depression of bone marrow activity is present during the persistence of severe renal disease.

AUTHORS.

Boyd, L. J., and Scherf, D.: The Electrocardiogram in Acute Emetine Intoxication.
J. Pharmacol. & Exper. Therap. 71: 362, 1941.

The alterations of the electrocardiogram after the intravenous administration of emetine hydrochloride were studied in dogs and cats.

Disturbance of intraventricular conduction is the most common change observed under these circumstances. Bradycardia and prolongation of atrioventricular conduction time develop regularly, but they are not pronounced.

If the intravenous dose does not exceed 37 mg. in dogs weighing 5 to 9 kg., the electrocardiographic alterations gradually disappear within forty-five minutes. Cardiac dilatation, especially involving the right ventricle, the development of which is simultaneous with the ventricular conduction disturbances, also vanishes within the same period.

The action of emetine is cumulative since much more pronounced effects result from the second or third injection of an equal amount of the drug although the normal electrocardiogram has been restored.

The most common arrhythmias to develop are auricular extrasystoles and auricular tachycardias. Alternation of the ventricular complexes is frequently observed during the tachycardia. Advanced stages of intoxication are required for the production of ventricular extrasystoles. Heart block with dropped beats was encountered only in cats.

AUTHORS.

Campbell, H. E.: The Statistical Method. A Vital Tool in Clinical Medicine.
Surgery 9: 825, 1941.

Clinicians have almost entirely neglected criteria of statistical analysis in their scientific writings. The many contradictory teachings and controversial practices originate in part in this neglect of well-recognized statistical procedure.

We have described in detail the derivation and application of the simpler formulas as they relate to percentages. With a little thought every doctor can master this technique and apply it in a very few minutes to medical papers which utilize percentages in their conclusions.

As presented now, most case series are too brief for sound conclusions. Publication should be withheld until longer series are amassed. A standard classification in such diseases as are now the center of controversy would enable short series to be combined and allow reliable conclusions to emerge.

Medical students should receive formal education in statistical procedure. Medical editors should demand of medical authors that their figures and data be statistically sound.

AUTHOR.

Book Reviews

SYNOPSIS OF DISEASES OF THE HEART AND ARTERIES: By George R. Herrmann, M.D., Professor of Medicine, University of Texas. The C. V. Mosby Co., St. Louis, 1941, Ed. 2, 468 pages, 91 illustrations, \$5.00.

Those not familiar with the first edition of this book might easily be misled by the term "Synopsis" into expecting a small brochure containing a very brief tabular summary of the most important facts relating to cardiac and arterial disease. The book is small in format, and might easily fit in the pocket of an overcoat, but it contains 450 pages of text, which is equivalent to 300 or more pages of the standard octavo volumes. It is in fact a synopsis, but a very full and extensive one.

To those engaged in study or practice in this field of medicine the author is well known for his many contributions to its advancement. To all such it is unnecessary to say that he speaks with the authority born of long experience as an investigator, teacher, professor of medicine, and consultant in active practice. This experience has fitted him admirably to survey the broad field of cardiovascular diseases and sift out of the formidable mass of material that which is really important and useful for advanced students and practitioners. The first edition of the book seemed to this reviewer the best summary of the subject that had ever appeared in English, and the present (second) edition fully sustains the splendid reputation of its predecessor.

To read the volume through from beginning to end is to discover a fault that is probably inevitable in a book of this type, intended primarily for reference. There is a certain amount of repetition in the discussion of related topics which would not be apparent in reading a single section or chapter. The only other adverse criticism that I would offer is that more space is devoted to chronic cardiac valvular disease (with separate chapters on aortic, mitral, and tricuspid valvular disease) than seems warranted in view of the current belief that etiology and functional condition are vastly more important than structural lesions.

There is no important aspect of cardiovascular disease that is omitted. The discussions are clear, comprehensive, authoritative, and up to date. If the author differs from other authorities in certain respects, it is almost invariably upon matters that are still unsettled, and his opinion may well be the correct one.

The book is cordially commended to all who desire a brief, authoritative discussion of the diagnosis and treatment of cardiovascular diseases.

H. M. MARVIN.

YOUR HEART: By Joseph M. Stein, M.D. Alliance Book Corporation, New York, 1941, 240 pages, \$2.75.

This book is designed for the laity, and presents much worth-while information concerning the heart, its function, and the diseases to which it is subject. It is predominantly optimistic in its approach, and does not present the material in such a manner as to frighten the cardiac patient, but offers encouragement to those who follow the regime outlined. The suggestions on the mode of life, the mental attitude, occupations, and avocations, and the general regimen to be followed are

helpful, but the book in no way attempts to prescribe for the patient. The endeavor to create popular appeal has led the author to a verbose and flowery presentation of some features in the early chapters, but this style does not persist throughout.

The implications which are made as to the effect of diseases of the teeth and tonsils on heart disease do not seem to be justified, and the relationship between angina pectoris and coronary artery disease is probably more close than is implied in the book. The results of surgical procedures on the heart do not yet justify the author's optimistic reports, especially in respect to those designed to remedy the effects of coronary occlusion. The best and most important features are the advice and encouragement offered to those patients with early or mild cardiac disease.

W. M. FOWLER.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. PAUL D. WHITE
President

DR. ROY W. SCOTT
Vice-President

DR. T. HOMER COFFEN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

*DR. EDGAR V. ALLEN	Rochester, Minn.	*DR. EDWIN P. MAYNARD, JR.	Brooklyn
DR. T. HOMER COFFEN	Portland, Ore.	*DR. THOMAS M. MCMILLAN	Philadelphia
DR. CLARENCE DE LA CHAPELLE	New York City	DR. JONATHAN MEAKINS	Montreal
DR. WILLIAM DOCK	San Francisco	DR. E. STERLING NICHOL	Miami
DR. HUGH FARRIS, St. John, N. B., Canada		DR. FRANKLIN R. NUZUM	Santa Barbara
DR. NORMAN E. FREEMAN	Philadelphia	*DR. STEWART R. ROBERTS	Atlanta
DR. GEORGE R. HERRMANN	Galveston	*DR. ROY W. SCOTT	Cleveland
DR. T. DUCKETT JONES	Boston	DR. FRED M. SMITH	Iowa City
*DR. WILLIAM J. KERR	San Francisco	*DR. HOWARD B. SPRAGUE	Boston
DR. EMANUEL LIBMAN	New York City	DR. WILLIAM D. STROUD	Philadelphia
DR. DREW LUTEN	St. Louis	*DR. PAUL D. WHITE	Boston
DR. GILBERT MARQUARDT	Chicago	DR. FRANK N. WILSON	Ann Arbor
*DR. H. M. MARVIN	New Haven	*DR. IRVING S. WRIGHT	New York City
		DR. WALLACE M. YATER	Washington, D. C.

DR. H. M. MARVIN, *Chairman, Executive Committee*
and Acting Executive Secretary

GERTRUDE P. WOOD, *Office Secretary*

TELEPHONE CIRCLE 5-8000

THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-seven physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$11.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

•*Executive Committee.*

The American Heart Journal

VOL. 22

DECEMBER, 1941

No. 6

Original Communications

INTERMITTENT CLAUDICATION AS A RESULT OF ARTERIAL SPASM INDUCED BY WALKING

WILLIAM V. LEARY,* M.D., AND EDGAR V. ALLEN, M.D.
ROCHESTER, MINN.

THE syndrome of intermittent claudication as a result of arterial spasm alone has been regarded as unlikely by most students of the peripheral circulation. With two exceptions, the existence of such a syndrome has been ignored almost entirely in textbooks on vascular diseases and other medical writings. In 1922, Thomas,¹ a Frenchman, wrote that a brief period of arterial spasm after muscular exercise was noted in some cases in which the circulation was otherwise normal and that this spasm was followed immediately by vascular dilatation. Pearl,² in 1937, reported six cases in which there were symptoms of arterial insufficiency caused by arterial spasm. In his cases, the onset of pain was definitely associated with acute ischemia of the feet and diminution or disappearance of pulsations in the arteries of the feet as a result of exercise. Relief of pain coincided with return of normal color of the skin and pulsations of the arteries. In all of the cases reported by Pearl, normal or nearly normal vasodilatation occurred as a result of anesthetization of peripheral nerves. There have been reports of other cases of intermittent claudication, with a normal vasodilatation response and normal pulsations in the peripheral arteries, but the authors fail to state whether or not pulsations in the arteries disappeared as a result of walking.^{3, 4} Veal⁵ has shown by arteriographic studies that intermittent claudication may affect patients whose large arteries are patent throughout their course and have normal lumens. He felt that the defect in the circulation which caused intermittent claudication was in the small arterial branches, which were few in number, irregularly distributed, and considerably shorter than normal. We have ordinarily

From the Division of Medicine, Mayo Clinic, Rochester.

Received for publication May 2, 1941.

*Fellow in Medicine, Mayo Foundation.

considered this the explanation for the intermittent claudication which affects patients whose circulation seemed normal during rest.⁵ The syndrome of intermittent claudication as a result of arterial spasm induced by exercise is unusual, for almost invariably exercise causes arterial dilatation instead of spasm.⁶⁻⁸

In the past year we have observed four patients who had this syndrome.

REPORT OF CASES

CASE 1.—A man, aged 44 years, first registered at the Clinic in 1935. At that time the patient complained primarily of epigastric distress suggestive of ulcer, but he also stated that for two years prior to registration he had noted a peculiar type of muscular exhaustion in the entire left leg which was precipitated by strenuous walking and promptly relieved by resting. Examination did not disclose evidence of neurologic disease, and the arteries of the lower extremities pulsated normally. Because of the mild character of the symptoms, further investigations were not made.

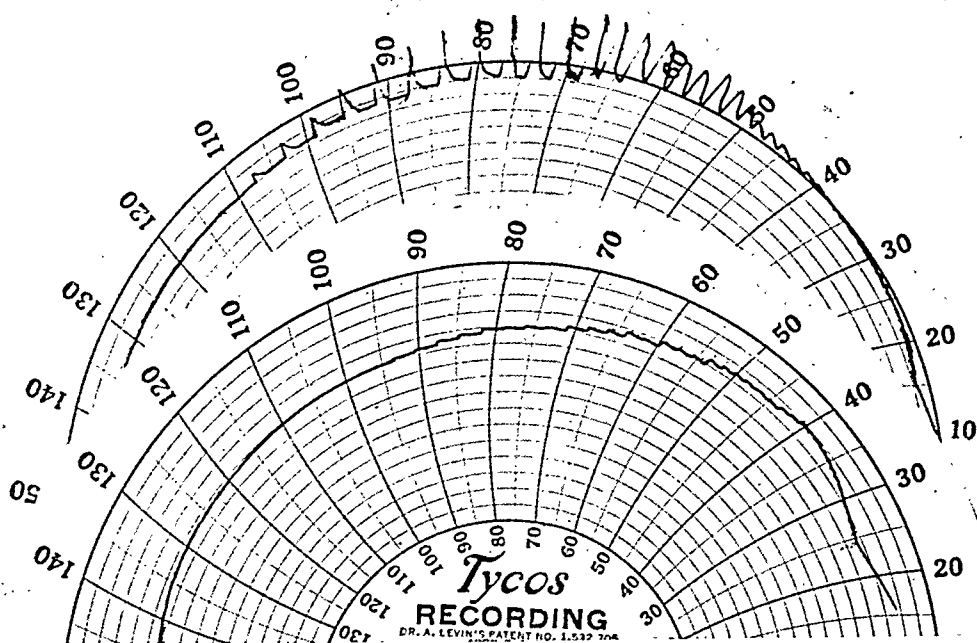


Fig. 1.—Case 1. Oscillometric records taken above the ankle; *upper record*, normal arterial pulsations when the patient was at rest; *lower record*, almost complete absence of arterial pulsations forty-five seconds after cessation of exercise.

The patient returned to the Clinic in 1939; he complained primarily of weakness which involved both legs and the trunk caudad to the level of the third lumbar vertebra. The weakness was present only after walking approximately 100 yards (91 meters) and was so severe that he was forced to stop for about a minute; the weakness then would disappear completely. By slowing his pace, he was able to walk indefinitely.

General physical examination disclosed nothing abnormal, with the exception of the peripheral circulation. The pulsations of the dorsalis pedis and posterior tibial arteries were normal when the patient was at rest. After exercise, pulsations in these arteries disappeared entirely, but reappeared about a minute after cessation of exercise. When the patient was at rest, a systolic murmur was audible over the

lower portion of the abdomen; its maximal intensity was at the midline just below the umbilicus, and its maximal transmission was to the femoral arteries. After exercise, a thrill was palpable over these arteries. The results of oscillometric studies made just below the knees confirmed the clinical observations (Figs. 1 and 2). Pulsations disappeared entirely after the patient walked up and down stairs rapidly for a minute; the return of pulsations corresponded roughly to the disappearance of symptoms. Surprisingly, the weakness of which he complained did not result from the exercise. Laboratory examination was essentially negative.

As a result of an intravenous injection of 25,000,000 killed typhoid bacilli, the temperature of the skin of the toes of the right and left feet increased from 25.2 to 34° C., and from 25.4 to 34.2° C., respectively. We consider that these increases in the temperature of skin as a result of fever induced by typhoid vaccine indicate a normal arterial circulation. When the patient still had fever and the temperature of the skin of the first toes was maximal, exercise induced arterial spasm.

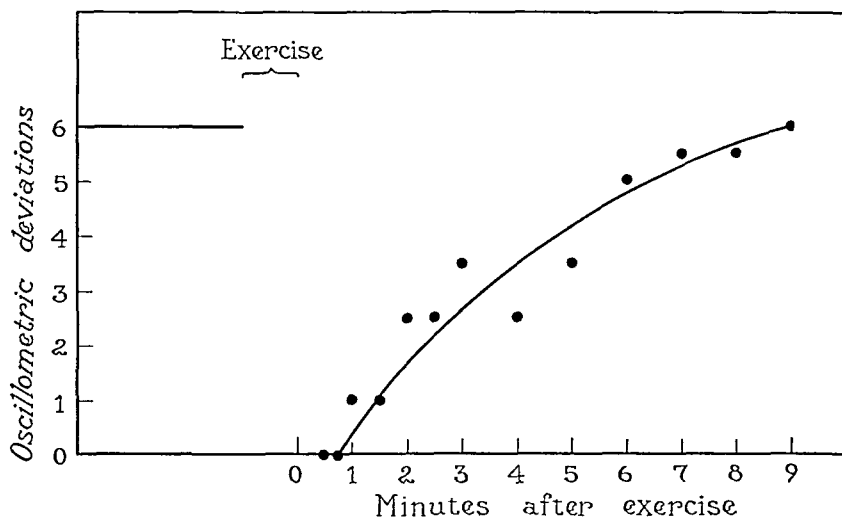


Fig. 2.—Case 1. Oscillometric deviations, taken above the ankle, of 6 units before exercise indicate normal arterial pulsations, and complete absence of oscillations immediately after exercise indicate absence of arterial pulsations. The pulsations, however, gradually returned to normal eight minutes after cessation of exercise.

The patient returned to the Clinic in April, 1940. He stated that since his last examination he had had rather severe and constant lumbar backache; two attacks of severe pain had occurred suddenly in the lumbosacral region; this pain had been crampy in character and so severe that he had gone to bed. The first attack had lasted an hour, and the second one, ten days.

Results of general physical examination were negative except for the circulation in the legs. Calcification of the abdominal aorta was evident roentgenologically. Pulsations were normal in the radial and ulnar arteries, moderately diminished in both femoral and the left popliteal arteries, greatly diminished in both posterior tibial and left dorsalis pedis arteries, and absent in the right popliteal and dorsalis pedis arteries. A systolic bruit was audible over the abdominal aorta.

A tentative diagnosis of dissecting aneurysm of the abdominal aorta was made.⁹ That such a condition might be present was suggested by the systolic murmur over the aorta in the lower portion of the abdomen, by the two attacks of severe pain, by occlusion of arteries of the legs which had not been occluded at the time of the first examination of the patient, and by the roentgenologic evidence of sclerosis of the abdominal aorta which was noted after the second examination. The presence or absence of dissecting aneurysm could be determined, of course, only

at necropsy. Whatever the etiology of the spasm of the arteries of the lower extremities, the spasm unquestionably caused the syndrome of intermittent claudication.

CASE 2.—A Jewish man, aged 32 years, was examined at the Clinic in January, 1940. The patient had had swelling of both legs during the five years prior to registration. This was the result of thrombosis of the inferior vena cava, which had occurred in the course of convalescence from pneumonia. In addition, intermittent claudication had been present in the right calf for five years and in the left calf for two years. Walking 100 to 500 yards (91 to 462 meters) produced the distress, and rest relieved it in about a minute. It never occurred during rest or standing.

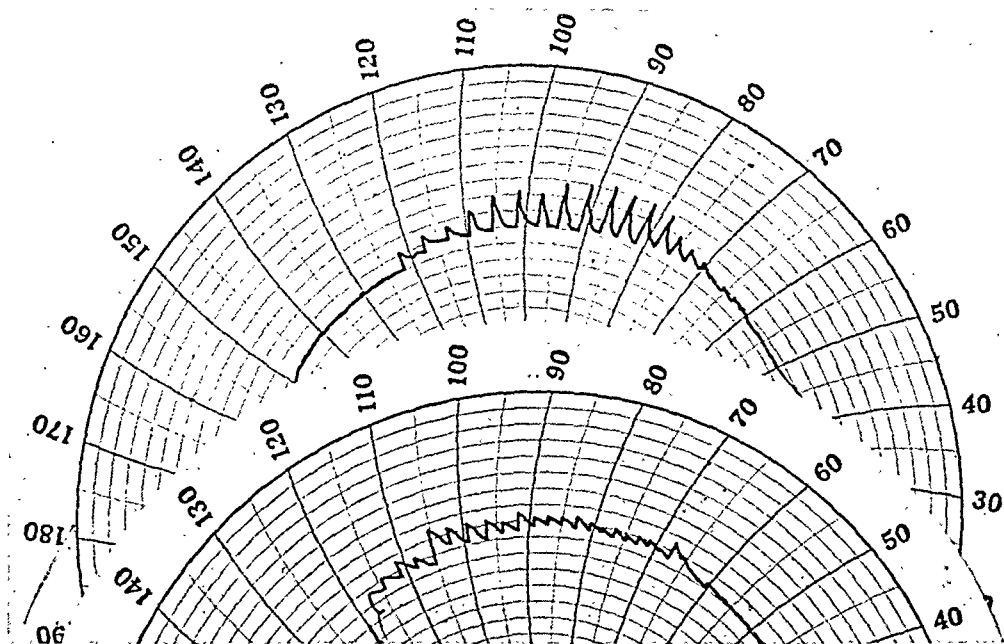


Fig. 3.—Case 2. Oscillometric records taken above the ankle: *upper record*, normal arterial pulsations when the patient was at rest; *lower record*, almost complete absence of arterial pulsations about one minute after cessation of exercise.

On physical examination, an extensive collateral venous circulation that involved both lower extremities, the abdomen, and the thorax to a level 2 inches (5 cm.) above the nipple line was noted. The arteries of the lower extremities pulsated normally except that pulsations could not be felt in either dorsalis pedis artery. As a result of walking rapidly for about a minute, pulsations in the posterior tibial arteries disappeared, but returned to normal after about four minutes of rest. The results of routine laboratory study were negative except for serologic tests for syphilis, which were equivocal and were not regarded as significant. Roentgenologic examination of the thorax disclosed nothing abnormal.

The results of oscillometric studies made just above the ankles confirmed the clinical observation of diminished arterial pulsations as a result of walking (Fig. 3). Walking caused the normal increase in pulsations in the region of the calf of the leg. Intramuscular injections of a complex pancreatic preparation (padutin) and the oral administration of alcohol, alone or in combination with the application of a rubber bandage to the legs, were found to increase the distance the patient could walk before claudication occurred. The use of the rubber bandage alone had an opposite effect. The claudication was invariably accompanied by a definite absence of pulsation in the posterior tibial arteries, as ascertained by

palpation. Decreased oscillations were also invariably associated with the intermittent claudication, and, as the symptoms disappeared with rest, the pulsations were found to return to normal.

CASE 3.—A man, aged 32 years, registered at the Clinic in January, 1940. The patient complained chiefly of chronic venous insufficiency which resulted from thrombophlebitis of the right leg after an appendectomy in 1931. He also complained of cramping distress of the right calf, which occurred after walking four or five blocks or on prolonged standing. The distress was relieved by resting for ten minutes and could be prevented by wearing a tight bandage on the calf. The distress was not characteristic of intermittent claudication; indeed, it seemed more probable that it was caused by the chronic venous insufficiency. However, if the patient walked, the pulsations in the right dorsalis pedis and posterior tibial arteries disappeared and could not be felt for about a minute after cessation of exercise, whereas pulsations in the same arteries in the left leg were unchanged as a result of walking.

CASE 4.—A man, aged 60 years, registered at the Clinic in March, 1940. For fifteen years he had had rather mild, low back pain, with extension to both hips. Two years prior to examination the pain had become sharp and rather severe and had begun in both gluteal regions, with extension upward to the lumbar region and to both hips and thighs. The distress, which was associated with a pulling sensation in both calves, was produced only by walking and was relieved almost immediately on stopping. The results of general physical examination were negative except for abnormalities relative to the arteries of the legs. When the patient was at rest, all of the arteries pulsated normally. After walking, which produced pain, the skin of the left foot became pale and the veins collapsed. The right foot remained normal in these respects. When the feet were elevated, there was moderate pallor of the skin of the left foot, and, when the feet were dependent, normal color returned slowly to the left foot. A soft, blowing, systolic bruit was audible over the abdomen 2 to 3 cm. below the umbilicus. This bruit was well localized during rest, but after exercise it was transmitted to both femoral regions.

Routine laboratory examinations of the blood and urine revealed no abnormalities. The lipoids in the blood, in milligrams per 100 c.c. of whole blood, were as follows: cholesterol, 235; cholesterol esters, 146; lecithin, 225; fatty acids, 376; and total lipoids, 611. Roentgenologic examination of the thorax revealed nothing abnormal; roentgenologic examination of the lumbar portion of the spinal column revealed hypertrophic changes and calcification of the abdominal aorta. When the patient rested in a room in which the temperature was 32.2° C., the temperature of the skin of the first and third toes of the right foot increased to 35° C. and 34.4° C., respectively, and the temperatures of the first and third toes of the left foot were 33.9° C. and 33.2° C., respectively. These studies indicated impaired circulation to the left foot. The results of examination with the oscillogram were normal for the right leg, both at rest and after exercise. Pulsations in the left calf were definitely diminished in periods of rest and after exercise were absent for approximately a minute.

COMMENT

We feel that the distress of these four patients was the result of diminished blood flow to the extremities. The diminution of blood flow definitely resulted from spasm of arteries, but we cannot explain why spasm occurred, for the usual arterial response to exercise is arterial dilation. However, systolic bruits were heard over the abdominal aortas

in Cases 1 and 4. Since the discovery of the bruit in Case 1, one of us (Leary) has examined routinely all patients for its presence, with entirely negative results. It seems to us, therefore, that such bruits indicate the presence of arterial disease. Roentgenograms of the abdominal aortas of these two patients revealed calcification. The similarity of the murmurs in Cases 1 and 4 to those produced by proved aneurysms was striking and caused us to suspect that such a lesion existed in each case. Since an aneurysm may cause interference with peripheral blood flow, it may be concluded that the circulatory disturbance observed in these cases was caused by an aneurysm, but just how such a disturbance is provoked remains unexplained.

The other two patients had had thrombophlebitis, and, at the time of examination at the Clinic, had chronic venous insufficiency. It occurred to us that venous obstruction might cause arterial spasm during exercise, but, when we had eight normal subjects run with the venous circulation obstructed by means of a tourniquet about the thigh, the pulsations in the arteries of the foot did not decrease or disappear. Also, one of us (Leary) studied the peripheral arterial pulsations, by means of an oscillometer, of twenty-five normal subjects and of eight patients who had *chronic occlusive arterial diseases, both before and after exercise*. In each case the arterial pulsations remained unchanged or actually increased as a result of exercise.

Acute thrombophlebitis occasionally causes absence of arterial pulsations in the affected extremity as a result of arterial spasm provoked by phlebitis. This arterial spasm apparently results from proximity to inflammation or from extension of inflammation from a vein to an artery. Such arterial spasm is, however, transient, and, in our experience, lasts but a few hours at the most. It is probable, however, that the residue of acute thrombophlebitis produced a "reverse sensitivity" of the arteries in our two cases, so that they contracted, instead of dilated, when the patient exercised. As far as is known, this is a new observation relative to arterial spasm. The exact explanation, however, remains obscure, although the clinical facts are impressive. Intermittent claudication can occur when patients walk because the arteries to the legs contract rather than dilate. This paradoxical reaction of arteries has, in our experience, indicated some disease of the arteries or veins. Whenever a patient relates a conclusive story of intermittent claudication, the physician must not exclude occlusive arterial disease as the cause of it because the arterial pulsations are normal, but he must suspect that the symptom of intermittent claudication is due to arterial spasm induced by walking, and he must study the pulsations in the arteries, both before and after exercise. If he fails to find evidence of a paradoxical reaction of the arteries, he may then consider localized obliteration of smaller arteries, as described by Veal.

REFERENCES

1. Thomas, André: L'angiospasme provoqué dans les artérites périphériques et la claudication intermittente, *Presse méd.* 2: 1049, 1922.
2. Pearl, F. L.: Angiospastic Claudication. With a Report of Six Cases, *Am. J. M. Sc.* 194: 505, 1937.
3. Morton, J. J., and Scott, W. J. M.: The Quantitative Determination of Vasoconstrictor Spasm as a Basis for Therapy in Peripheral Arterial Diseases, *Ann. Surg.* 96: 754, 1932.
4. Horton, B. T.: Intermittent Claudication in the Extremities With Pulsating Vessels, *M. Clin. North America* 14: 783, 1930.
5. Veal, J. R.: The Pathologic Basis for Intermittent Claudication in Arteriosclerosis, *AM. HEART J.* 14: 442, 1937.
6. Lewis, T.: Pain in Muscular Ischemia; Its Relation to Anginal Pain, *Arch. Int. Med.* 49: 713, 1932.
7. Veal, J. R., and McFetridge, Elizabeth M.: Vascular Changes in Intermittent Claudication: With a Note on the Value of Arteriography in This Symptom Complex, *Am. J. M. Sc.* 192: 113, 1936.
8. McDowall, R. J. S., Malcolmson, G. E., and McWhan, I.: The Control of the Circulation of the Blood, New York, 1938, Longmans, Green & Co., 619 pp.
9. Glendy, R. E., Castleman, Benjamin, and White, P. D.: Dissecting Aneurysm of the Aorta; a Clinical and Anatomical Analysis of Nineteen Cases (Thirteen Acute) With Notes on the Differential Diagnosis, *AM. HEART J.* 13: 129, 1937.

SYSTOLIC GALLOP RHYTHM

SHIGEAKI HINOHARA, M.D.

KYOTO, JAPAN

SINCE Cüffer and Barbillon¹ first described systolic gallop rhythm, in 1887, other investigators have dealt with it. Systolic gallop rhythm is produced when an extra sound falls between the first and the second heart sounds. As to the extrasystolic sounds, various authors have included different sounds under this designation.

Systolic gallop rhythm is divided into three classes, as follows: (1) so-called systolic gallop rhythm (Potain,² Wolferth and Margolies³), (2) systolic click, and (3) systolic pericardial knock.

Potain² observed systolic gallop rhythm in cases of typhoid fever, typhoidlike influenza, and arteriosclerosis with aortic atheroma. He stated that the extra sound was heard best over the aortic area, and regarded it as an arterial phenomenon caused by diminished elasticity and tonicity of the aorta. He recognized systolic gallop rhythm solely by auscultation, but Wiedemann⁴ and Wolferth and Margolies³ obtained graphic records of systolic gallop rhythm, and established proof of its existence, as designated by Potain.

According to Wolferth and Margolies,³ there are at least two types of systolic gallop sound, exclusive of various other types of sounds which may fall between the first and the second heart sounds, namely, aortic systolic gallop rhythm and apical systolic gallop rhythm; in the former the extra sound is heard best over the aortic area, as described by Potain² and Pawinski,⁵ and in the latter it is heard best over the apex. They stated that the extra sound in aortic systolic gallop rhythm is produced in the aorta, that is to say, it is caused by sudden checking of the distention of the aortic wall during systole or by impact of the aorta against surrounding structures at that instant. They recognized this kind of extra sound in cases of hypertensive cardiovascular disease, aortic insufficiency, and miliary tuberculosis. As to the apical systolic sound, they stated that the impact of the cardiac apical region against the chest wall may be concerned in the mechanism of its production.

The character of the systolic click is quite different from the systolic gallop sound mentioned above. It is a kind of crepitant noise of very short duration, and usually it is high pitched. Gallavardin⁶ and Johnston⁷ stated that the click is caused by tugging on pleuropericardial ad-

From the Third Medical Clinic of Kyoto Imperial University. Director, Professor Toshikazu Mashimo, M.D.

Received for publication March 14, 1941.

hesions during systole, and it was called by Lian and Deparis⁶ "le *claquement meso-systolique pleuropericardique*." This extra sound has no clinical significance and has nothing to do with organic heart diseases. According to Johnston,⁷ it is of maximum intensity at or near the apex, and its loudness changes with respiration or shift of position.

As to the extra sound which produces systolic gallop rhythm, there is another type, called the pericardial knock, which has many features in common with the systolic click. Pericardial knock has been the subject of research by various authors, including Rees and Hughes,⁹ Smith,¹⁰ Munden,¹¹ and Lister.¹² It is a short sound, and commonly louder than the click. This sound is heard occasionally after spontaneous left-sided pneumothorax, or during the therapeutic induction of left-sided pneumothorax. It is heard best at the apex and is influenced by respiration and by position. According to Barnwell and Greene,¹³ it is produced when a highly active heart whose movement is not limited or cushioned by lung tissue strikes either the chest wall or the diaphragm.

We have been recording heart sounds during the past two years, and encountered ten cases of systolic gallop rhythm of various types, as follows:

A. Three cases of systolic click (one patient had mitral disease; two had no cardiac disease).

B. Two cases of systolic pericardial knock (both patients were under observation during the induction of left-sided pneumothorax).

C. Four cases of so-called systolic gallop rhythm (one patient had aortic insufficiency; two had mediastinal tumors; and one had a patent ductus arteriosus and combined mitral disease).

D. One case of auricular systolic gallop rhythm (sinoauricular block with nodal extrasystole).

We shall here report only the cases of systolic gallop rhythm in groups C and D. In group C it was proved that the gallop rhythm was caused by a mediastinal tumor in two cases. Moreover, it was shown that there may be pulmonic systolic gallop rhythm, as well as aortic and apical systolic gallop rhythm.

METHOD

For the graphic registration of the heart sounds we employed Koizumi's¹⁴ apparatus, which is an application of high frequency current. The apparatus consists of five components, namely, a microphone, an oscillator, a detector, an amplifier, and an oscillograph. As a microphone, the author used a round metal plate (diameter, 3 cm.), insulated by a mica plate of the same size (thickness, 1 mm.) on one side; the metal plate was connected to the grid of the oscillator. This microphone is placed over the chest on its insulated side, and fixed by adhesive tape or a bandage. The microphone acts as the fixed plate of a condenser microphone, and the oscillating chest wall, which is earthed, acts as the oscillating plate of a condenser microphone.

Thus the change in electrical capacity between the fixed metal plate and the oscillating chest wall is received and magnified.

The author¹⁵ inserted an adequate electrical filter into the circuit and caused the apparatus to be sensitive to either higher or lower frequency sounds as desired (Fig. 1).

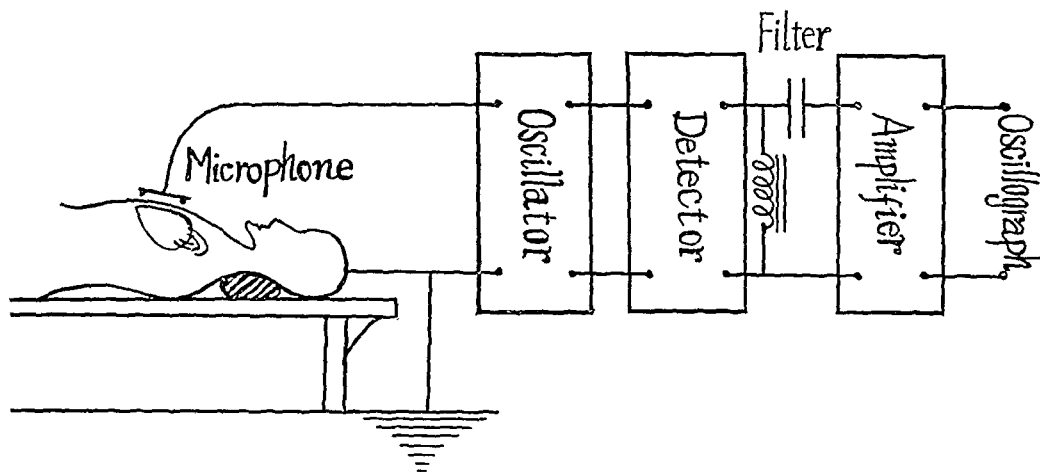


Fig. 1.—Diagram of the connection.

For recording the heart sounds through the esophagus, the following method was invented by the author.¹⁵ For a microphone an insulated piece of metal (length, 1.5 cm.; diameter, 4 mm.) was fixed to the end of a rubber tube similar to a duodenal tube. The metal piece was connected to the grid of the oscillator of Koizumi's apparatus by a fine wire through the tube. By having the patient swallow the microphone and fixing it at a certain height we can record the oscillations of the esophageal wall as the heart sounds; the principle is the same as that of the condenser microphone mentioned above.

The heart sounds were always recorded in conjunction with Lead II of the electrocardiogram, and the time markings were at $\frac{1}{100}$ second intervals.

REPORT OF CASES

CASE 1.—R. S. was a 36-year-old woman with aortic insufficiency. She had had diphtheria at the age of 10 and rheumatic arthritis at the age of 15.

The heart was moderately enlarged to the right and left. Over the aortic area, the base, and the apex, a systolic murmur and a blowing diastolic murmur were heard. A diastolic murmur followed the second aortic sound, and was maximum in intensity over the midsternal region. Moreover, an extra sound was heard between the first and the second heart sounds over the aortic area and at the apex. A capillary pulsation was present. The blood pressure was 160/40. The electrocardiogram showed left ventricular preponderance and evidence of myocardial damage (depressed S-T segment in Lead I).

Fig. 2 shows the heart sound tracings which were recorded over the aortic area. The extra sound (G) fell nearly midway between the first and second heart sounds, that is to say, 0.23 second after the Q wave and 0.18 second prior to the second heart sound. The tracing indicates that it is formed by two oscillations with a frequency of 50 per second.

CASE 2.—M. I. was a 58-year-old woman with a mediastinal tumor. She complained of cough, hoarseness, and edema of the upper half of her body. These symptoms began two months before her admission.

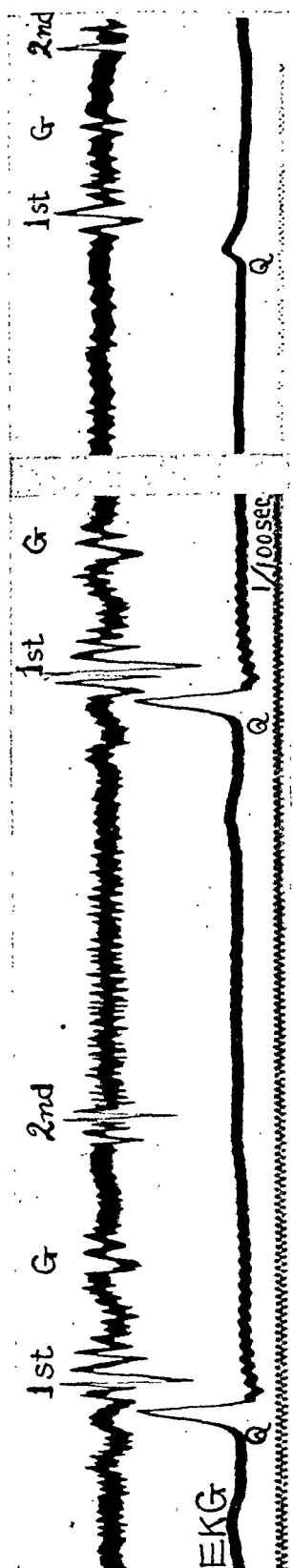
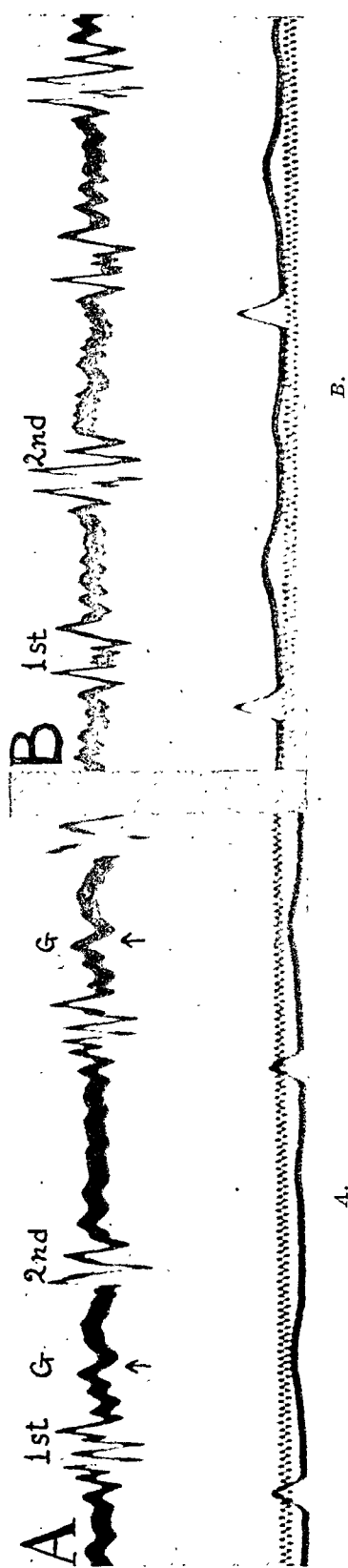


Fig. 2.

Fig. 2.—Case 1. Aortic insufficiency. Systolic extra sound (G) is clearly shown midway between the first and second heart sounds (recorded over the aortic area).

Fig. 3.

Fig. 3.—Case 2. Mediastinal tumor. Systolic gallop rhythm is present (recorded over the aortic area).



A.

B.

Fig. 4.—Case 3. Mediastinal tumor and pleuritis exsudativa sinistra. A was recorded before the withdrawal of the fluid; the systolic extra sound (inaudible), with low frequency, is recorded. B was recorded after the withdrawal of the fluid; no systolic gallop rhythm is shown.

Roentgenologic examination of the chest demonstrated a sharply demarcated, nonpulsatile mass in the right hilus. The heart was normal in size, and was of the dropped type. The aorta was markedly displaced to the left and upward by the mediastinal mass. The electrocardiogram showed depression of the S-T segment in Leads I and II and evidence of a drop heart. The blood pressure was 105/60. The sphygmogram revealed sclerosis of the radial artery.

Over the aortic area a soft systolic murmur and a weak, systolic, extra sound were heard. The heart sounds were recorded over the aortic area and at the apex. Systolic gallop rhythm was shown in both tracings. Referring to Fig. 3, the extra sound fell in the midsystolic phase, that is to say, 0.2 second after the Q wave and 0.11 second prior to the second heart sound. The extra sound in Fig. 2 was formed by two oscillations of a frequency of 50 to 60 per second, but the extra sound recorded over the apex was lower pitched, with a frequency of 30 to 40 per second, and it could not be recognized by auscultation.

CASE 3.—H. Y. was a 24-year-old man with a mediastinal tumor. He had had a cough for a year, which was explained by a doctor as due to a mediastinal tumor. Eleven months later it was accompanied by pleuritis exsudativa sinistra.

Physical examination prior to withdrawal of the pleural effusion showed that the apex impulse was not perceptible. The left border of cardiac dullness could not be located because of the pleural effusion on the left. The right border extended to the right margin of the sternum. The first and the second heart sounds were pure. The blood pressure was 120/60.

Physical examination after 1,000 c.c. of the pleural effusion had been removed showed that the left border of cardiac dullness was 2 cm. medial to the left nipple line, and that the right border was at the midsternal line. The first heart sound was somewhat muffled. The blood pressure was 120/40.

The electrocardiogram revealed a tendency toward right ventricular preponderance and evidence of slight myocardial damage. Roentgenologic examination of the chest showed a mass in the mediastinum which was diagnosed as a mediastinal tumor.

Heart sounds were recorded twice, that is, before (Fig. 4A) and after (Fig. 4B) removing the pleural effusion. In Fig. 4A an extra oscillation, with a frequency of 30 per second, is apparent between the first and second heart sound; it fell 0.18 second after the Q wave and 0.12 second prior to the second heart sound. In Fig. 4B no extra sound was present in the systolic phase.

CASE 4.—K. Y. was a 16-year-old girl with a patent ductus arteriosus and combined mitral failure.

The patient had complained of palpitation since her childhood. At the age of 15 years she had rheumatic arthritis. For one month previous to entering the hospital she complained of palpitation and cough and was confined to her bed.

The heart was greatly enlarged, and the apex impulse was thrusting and heaving in the sixth intercostal space 5 cm. to the left of the nipple line. The left border of cardiac dullness coincided with the apex beat. The right border of dullness was just to the right of the sternum. In the pulmonic area, that is, in the second intercostal space near the left of the sternum, abnormal dullness was recognized and pronounced thrills were felt. Over the pulmonic area a midsystolic extra sound was heard, together with a harsh systolic murmur and a weak diastolic murmur. The pulmonic second sound was accentuated. Over the apex a blowing systolic murmur, a low-pitched, rumbling, diastolic murmur, and a third heart sound were heard. Over the aortic and tricuspid areas and the base, systolic and diastolic murmurs,

decreasing in loudness, were heard. But no systolic extra sound was heard over any of the auscultatory areas except the pulmonic. When the aorta abdominalis was compressed forcibly with the hand, the pulmonic systolic murmur increased in loudness and the pulmonic second sound became more accentuated. Valsalva's test was positive.

Roentgenologic examination showed marked enlargement of the cardiac silhouette, both to the left and right, and marked prominence of the pulmonary arc (Fig. 5). The electrocardiogram revealed right ventricular preponderance and evidence of coronary insufficiency. The blood pressure was 115/30. Physical exertion caused marked elevation of the maximum pressure and depression of the minimum pressure.



Fig. 5.—Case 4. Roentgenogram taken at the time when the systolic extra sound was heard over the pulmonic area and the heart had been failing. Note the prominence of the pulmonary arc and enlargement of the heart to the left and right.

In the lung there were moist râles. The liver was enlarged. The physical signs were thought to indicate that the patient was suffering from congestive heart failure caused by patency of the ductus arteriosus and combined mitral disease.

Heart sounds were recorded over various auscultatory areas. Over the pulmonic area the systolic extra sound was conspicuous (Fig. 6). This extra sound was formed of oscillations of a frequency of 132 per second, and it fell 0.19 second after the Q wave and 0.19 second prior to the second heart sound.

The second examination was done a month later, when she had recovered from serious cardiac failure, but at this time no systolic gallop rhythm was demonstrated in the heart sound tracing. The roentgenogram revealed that the heart was slightly diminished in size, and that the pulmonary arc was not so conspicuously projected as at the first examination.

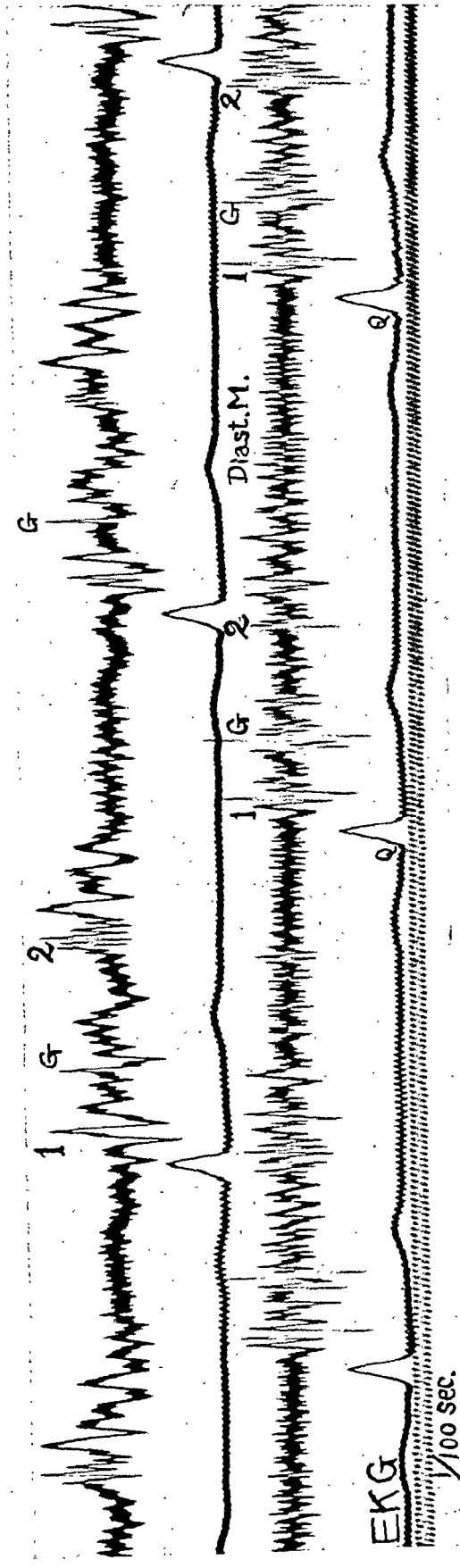


Fig. 6.—Case 4. Patent ductus arteriosus and combined mitral disease. The systolic extra sound (G) was present only over the pulmonic area. Upper: using no filter. Lower: using a filter. The systolic extra sound is clearly shown.

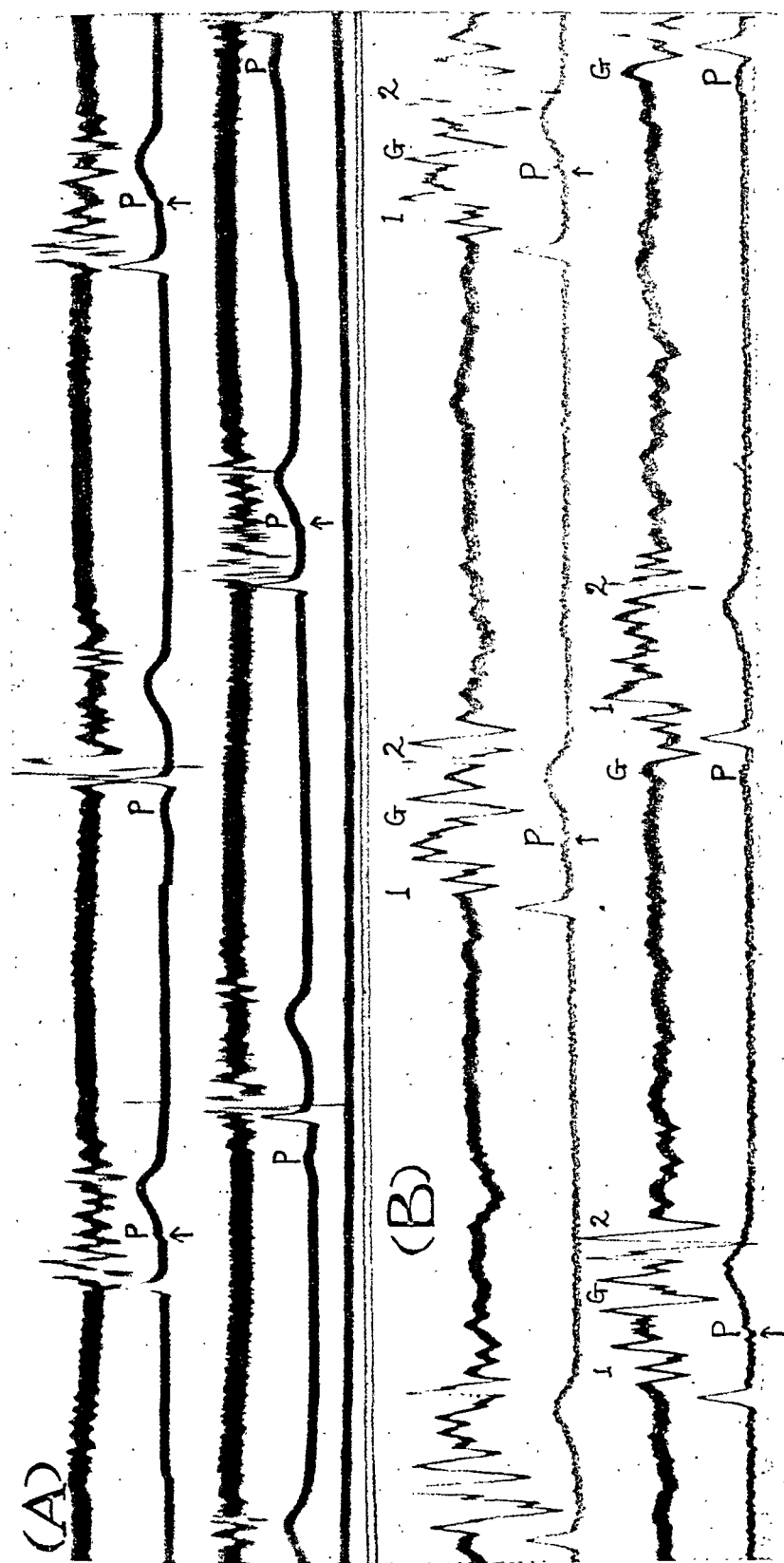


Fig. 7.—Case 5. Incomplete sinoauricular block and nodal extrasystoles. A: recorded over the precordium. Upper: using no filter. Lower: using a filter. The systolic extra sound (inaudible) is recognized as a mere trace on the upper strip. B: recorded through the esophagus at a distance of 33 cm. from the front teeth, using no filter. The sound marked as G is due to the auricular contraction. When the P wave of the electrocardiogram precedes the Q wave at a certain distance, the auricular sound (G) is heard as the presystolic gallop sound, as indicated by the last two beats in the lower strip. When the P wave, which is due to a nodal extrasystole occurs midway in the S-T segment, the auricular sound (G) falls between the first and the second heart sounds and systolic gallop rhythm is produced, as indicated by the second and the third beats in the upper strip and the first beat in the lower strip.

CASE 5.—Y. S. was a 36-year-old man with incomplete sinoauricular block and nodal extrasystoles. The pulse rate was 40. Except for bradycardia, he had no complaint.

The heart was normal in size and position. A moderately loud systolic murmur was heard over the apex and the base. The heart sound and murmurs varied in loudness. The electrocardiogram showed partial sinoauricular block, with nodal extrasystoles; there was evidence of myocardial damage, and the Q-T interval was prolonged to 0.49 second. The blood pressure was 140/70.

The heart sounds were recorded through the esophagus, as well as over the precordium. The esophageal heart sounds were obtained by placing the microphone in the esophagus at a distance of 33 cm. from the front teeth (Fig. 7B). The electrocardiogram revealed that the P wave was not uniform in its occurrence. When sinoauricular conduction was prolonged, the P wave was retarded in its occurrence and the P-Q interval was shortened. When sinoauricular conduction was blocked, the P wave appeared late in the S-T segment because of nodal extrasystoles.

Fig. 7B shows that the auricular sound corresponds to the P wave. When the P wave preceded the Q wave, the auricular sound was recognized as a presystolic gallop sound; whereas, when the P wave occurred late in the S-T segment, the auricular sound was recognized as a systolic gallop sound. The auricular systolic gallop sound was transmitted to the precordium also (Fig. 7A), but it was not so conspicuous there as in the esophagus.

DISCUSSION

We have reported five cases of systolic gallop rhythm of various types, exclusive of the systolic click and the systolic pericardial knock. Among them there were cases of gallop rhythm which was demonstrated solely in the sound tracings, and was not recognized by auscultation.

As to the genesis of systolic gallop rhythm, Potain² stated that it is caused by diminished elasticity and tonicity of the aortic wall. He believed that the aortic distension occurred quickly, but ceased suddenly, with tension and shock which were responsible for the sound. His theory was supported by Wolferth and Margolies,³ who stated that systolic gallop rhythm, as described by Potain, was found in some cases of hypertensive cardiovascular disease or aortic insufficiency.

The patient in Case 1 was suffering from aortic insufficiency, and this case may be properly said to belong to the type described by Potain and Wolferth and Margolies, but in Cases 2 and 3 there was neither a valvular defect nor hypertensive cardiovascular disease. In Case 2 there may have been sclerosis of the vascular system, but in Case 3 there was no sign of arteriosclerosis. A mediastinal tumor was recognized in both cases.

Roentgenologic examination in Case 2 revealed that the aortic arc was forced markedly to the upper left part of the heart by a tumor growing in the mediastinum. We believe that in this case the extrasystolic sound was produced by the sudden checking of distention of the distorted aorta.

In Case 3 systolic gallop rhythm was recognized in the tracing, but it could not be detected by auscultation because of the low frequency

and small amplitude. This extra sound disappeared after the pleural effusion was drained. In this case, also, a mediastinal tumor was recognized in the roentgenogram. We believe that at the first examination the mediastinal tumor and pleural effusion compressed the aorta and the heart in such a way that transmission of the aortic pulsation to the precordium was facilitated, thus causing a low and weak systolic extra sound.

In Case 4 the patient had congestive heart failure. In this case the systolic extra sound was heard over the pulmonic area only, and solely during the period when the heart was extremely enlarged and decompensated. The roentgenogram which was taken at the time when the systolic extra sound was present showed marked prominence of the pulmonary arc. The extra sound occurred 0.19 second after the Q wave and seemed to correspond with the aortic extra sound. From these observations we conclude that the pulmonic systolic sound might be produced by sudden checking of the distending movement of the hypertensive pulmonary artery, or by distention of the ductus arteriosus in the midsystolic phase. Wolferth and Margolies³ reported two types of systolic gallop rhythm, that is, aortic and apical, but the above case does not belong to either of them. It may be properly termed a type of pulmonic gallop rhythm.

In Case 5 there was systolic gallop rhythm of an entirely different nature, which should be called auricular systolic gallop rhythm. The author has stated already^{16, 17} that auricular contraction produces a low-pitched sound caused by oscillation of the auricular wall, in any phase of the cardiac cycle. This auricular sound is transmitted better to the esophagus than to the precordium. Fig. 5B shows the heart sound tracing which was obtained through the esophagus at a distance of 33 cm. from the front teeth, where the left auricle is in contact with the esophageal wall. The auricular sound was clearly shown to correspond to the P wave. Systolic gallop rhythm was present only when the auricular contraction occurred in the midsystolic phase. The genesis of this auricular gallop rhythm is very different from that of any other types of systolic gallop rhythm hitherto described, and has nothing to do with the character or the movement of the aorta, or of the pulmonary artery.

SUMMARY

1. Five cases of various types of systolic gallop rhythm are reported, exclusive of the systolic click and the systolic pericardial knock.
2. One case of aortic insufficiency was regarded as belonging to common type of systolic gallop rhythm described by Potain and Wolferth and Margolies.
3. Two of the patients had mediastinal tumors. In one case the systolic gallop sound was shown to be produced by displacement of the aorta by the tumor. In the other case the systolic gallop sound was

recorded only when the pleural effusion existed. The tumor and the effusion seemed to have something to do with the occurrence of the extra sound.

4. In one case of patent ductus arteriosus and combined mitral disease, systolic gallop rhythm was present temporarily over the pulmonic area only. This extra sound appeared to be produced by the pulmonary artery or the ductus arteriosus. The author considers it a type of pulmonic gallop rhythm.

5. One case of systolic gallop rhythm of an entirely different type is reported. This gallop sound was caused by interposition of the auricular contraction in the midsystolic phase, and it should be called an auricular systolic gallop rhythm. It was most conspicuous in records made from within the esophagus.

The author wishes to express his thanks to Prof. T. Mashimo, Dr. M. Maekawa, and Dr. H. Koizumi for permission to publish this report, and for their helpful criticism.

REFERENCES

1. Cüffer and Barbillon: Nouvelles recherches sur le bruit de galop, *Arch. gén. de méd.* 1: 129, 301, 1887.
2. Potain, P. G.: Le bruit de galop, *Semaine méd.* 20: 175, 1900.
3. Wolferth, C. C., and Margolies, A.: Systolic Gallop Rhythm, *AM. HEART J.* 19: 129, 1940.
4. Wiedemann, G.: Zur Frage des mesosystolischen Galloprhythmus, *Ztschr. f. d. ges. exper. Med.* 2: 297, 1914.
5. Pawinski, J.: *Ztschr. f. klin. Med.* 64: 70, 1907.
6. Gallavardin, L.: Pseudo-dedoublement du deuxième bruit du coeur simulant le dedoublement mitral par bruit extra-cardiaque tele-systolique surajoute; *Lyon méd.* 121: 409, 1913.
7. Johnston, F. D.: Extra Sounds Occurring in Cardiac Systole, *AM. HEART J.* 15: 221, 1938.
8. Lian, C., and Deparis, M.: Le Claquement meso-systolique pleuropericardique, *Bull. et mém. Soc. méd. d. hôp. de Paris* 49: 496, 1933.
9. Rees, W. A., and Hughes, G. S.: Wounds of the Chest as Seen at an Advanced Operating Centre, *Lancet* 1: 55, 1918.
10. Smith, S. M.: Pericardial Knock, *Brit. M. J.* 1: 78, 1918.
11. Munden, W. P. H.: Pericardial Knock, *Brit. M. J.* 1: 174, 1918.
12. Lister, W. A.: A Case of Pericardial Knock Associated With Spontaneous Pneumothorax, *Lancet* 1: 1225, 1928.
13. Barnwell, L. B., and Greene, J.: Quoted by Johnston, F. D., *AM. HEART J.* 15: 221, 1938.
14. (a) Koizumi, H.: Eine neue Methode der Registrierung des Spitzenstosses und Herztones, *Nippon J. Clin. Angio-cardiolog.* 4: 137, 1938.
(b) Koizumi, H.: Über die Verwendung einer neuen Methode der Kreislaufdiagnose mittels Anwendung von hochfrequenten electrischen Schwingungen, *Klin. Wchenschr.* 19: 1109, 1940.
15. Hinohara, S.: A New Method for the Recording of Heart Sounds and Murmurs, *Nippon J. Clin. Angio-cardiolog.* 6: 117, 1940.
16. Hinohara, S.: On the First Component of the Auricular Sound, *Nippon J. Clin. Angio-cardiolog.* 6: 319, 1940.
17. Hinohara, S.: Investigation of the Normal Heart Sounds Induced Through the Esophagus, With Special Attention to the Auricular Sound, *Nippon J. Clin. Angio-cardiolog.* 6: 159, 1940.

THE ESTIMATION OF CARDIAC OUTPUT FROM BLOOD PRESSURE AND PULSE WAVE VELOCITY MEASUREMENTS ON SUBJECTS WITH CARDIOVASCULAR DISEASE

I. CARDIOVASCULAR DISEASE OTHER THAN AORTIC REGURGITATION

H. C. BAZETT, M.D., L. B. LAPLACE, M.D., AND J. C. SCOTT, PH.D.
PHILADELPHIA, PA.

IN A PREVIOUS report from this laboratory,¹ it was shown that the stroke volume of the heart may be calculated for normal subjects by means of empirical equations, utilizing data obtained from optical records of arterial pressure, pulse wave velocity, and shape of the pulse, together with assumed volumes for the larger arteries. Estimates of cardiac output which corresponded closely with those obtained by the acetylene method were obtained on subjects of varying size and age and in the presence of physiologic variations in the cardiovascular system induced by meals,² hot and cold baths,³ and change of position.⁴ The present report is concerned with the estimation of cardiac output by this method on subjects with disease of the cardiovascular system other than aortic insufficiency.

There is an obvious need for a method by which the cardiac output may be ascertained with safety and accuracy on very ill patients. Gasometric methods are often not usable in such cases.

The method is based upon estimates of the pulse pressure and of the distensibility of the arterial system. An optical oscillogram is recorded from the upper arm, from which are obtained the lateral systolic, diastolic, and pulse pressures. Sphygmograms are recorded simultaneously from the subclavian, brachial, femoral, and dorsalis pedis arteries, together with a cardiogram from the upper sternum. From these records are obtained the pulse wave velocities from the heart to subclavian artery, subclavian to brachial artery, subclavian to femoral artery, and femoral to dorsalis pedis artery. From the sphygmogram of the brachial pulse are calculated the duration of systole and diastole* and (utilizing the blood pressure values obtained from the oscillogram) the mean pressure, not only in the whole cycle but also in its systolic and diastolic phases. From the subject's age and surface area

From the Departments of Physiology of the University of Pennsylvania and Hahnemann Medical College, and from the Philadelphia General Hospital.

Received for publication April 2, 1941.

*The divisions actually used are made on an arbitrary basis.

of the body the internal cross-sectional area of the ascending aorta is estimated (utilizing a graph based upon autopsy data¹). Then where:

V_s = Outflow from aorta in systole	Q = Cross section of aorta
V_d = Outflow from aorta in diastole	A = Surface area of body
M_s = Mean pressure in systole	H = Height of body in cm.
M_d = Mean pressure in diastole	$V_1 = Q \times 0.12H$
Z = Diastolic pressure	$V_2 = Q \times 0.15H$
D = Diastolic pressure	$V_3 = A \times 0.065H$
s = Duration of systole	$V_4 = A \times 0.34H$
d = Duration of diastole	
v_1 = P.W.V., heart to subclavian artery	
v_2 = P.W.V., subclavian to brachial artery	
v_3 = P.W.V., subclavian to femoral artery	
v_4 = P.W.V., subclavian to dorsalis artery	

$$(1) \quad V_d = \frac{12.7}{100} \left(\frac{V_1}{v_1^2} + \frac{V_2}{v_2^2} + \frac{V_3}{v_3^2} + \frac{V_4}{v_4^2} \right) (Z - D)$$

$$(2) \quad V_s = V_d \frac{s}{d} \frac{(M_s - 20)}{(M_d - 20)}$$

$$(3) \quad \begin{aligned} \text{Output per beat} &= V = V_d + V_s \\ \text{Output per minute} &= \text{Output per beat} \times \text{pulse rate} \\ \text{Cardiac index} &= \frac{\text{Output per minute}}{\text{Surface area}} \end{aligned}$$

The data also permit quantitative evaluation of other factors in the cardiovascular system.

1. *Effective Peripheral Resistance*.—Since the mean pressure is determined by the cardiac output and the effective resistance of the arterioles, if the first two are known, the arteriolar resistance may be expressed quantitatively, i.e., as the mean pressure divided by the cardiac index. For convenience, this value may be multiplied by 3, for, in so doing, the resultant value for normal young subjects is about 100 (70 to 130).

2. *Effective Distensibility of the Vessels*.—These measurements are obtainable from the equations, for the latter depend upon an estimation of the distensibility of the vessels which takes into account the compensatory effect of the larger aortic capacity of the older subjects. The values are expressed as the absolute increase in ml. per mm. Hg increase in pressure per square meter of body surface. They are derived from equation (1) by omitting $Z-D$ and dividing by the surface area.

The data available on apparently normal subjects indicate that the effective distensibility of the aorta increases with age, until the age of about 40, as the result of enlargement of the aorta. Values of the order of 0.65 and 0.95 are reached; after the age of 40 or 50 these values decrease again, as changes in the walls of the vessels outbalance the effects of increased size. On the other hand, the effective distensibility of the peripheral vessels progressively decreases with advancing age in normal subjects. However, present data are inadequate for the establishment of standards.

3. *Work of the Left Ventricle.*—Since the mean pressure during the period of systolic ejection is estimated, a more accurate calculation of the compression work of the left ventricle is possible. Normal values for the compression work of the left ventricle in a man of average size may be considered as about 4,150 Gm. cm. per beat per square meter, and about 2.9 kilogram meters per minute per square meter. Some improvement can also be attained in the calculation of work done in developing kinetic energy.

4. *Time Relations of Ventricular Contraction.*—Estimation of the pulse wave velocities requires determination of the beginning of ventricular expulsion. This point may be obtained with considerable accuracy, in our experience, by recording a cardiogram from the upper sternum. Such a cardiogram also affords criteria by which the duration of the various phases of cardiac contraction may be estimated. These have additional interest when correlated with the electrocardiogram.⁶

METHODS

Estimates of cardiac output from blood pressures and pulse wave velocities were made on fifteen subjects with abnormal cardiovascular systems, fourteen of whom were patients in the medical wards of the Philadelphia General Hospital, and one of whom was a medical student. The total number of observations was twenty-four. On six of the subjects, estimates of the cardiac output by the acetylene method were also made, either immediately after or before the blood pressure measurements. On the other subjects similar estimates by the acetylene method were attempted, but the procedure proved to be beyond their capacity. The case histories of all subjects are outlined.

In most cases the subjects were examined approximately two to three hours after a light breakfast, and after at least forty-five minutes' rest. Records of blood pressure and pulse wave velocity were made in the recumbent posture, unless a semi-recumbent posture was necessitated by orthopnea. The electrocardiogram was taken on a separate camera, and was synchronized by means of a signal which marked both records simultaneously. Measurements of vessel lengths for pulse wave velocity estimates were made with the subject completely recumbent. No allowance was made for tortuosities. The cardiac output was expressed in relation to the subject's contemporary surface area, as estimated from his weight. On the other hand, the volumes of the vessels were estimated from the subject's normal, rather than contemporary, weight. The difference between the two weights was due to recent changes, usually either edema or wasting.

For acetylene estimates a mixture was used which contained a high oxygen percentage (usually over 14 per cent in the final sample after rebreathing) and an initial concentration of about 3 per cent of CO₂. Three samples were taken for analysis, usually after eighteen, twenty-four, and twenty-nine seconds of rebreathing in the more ill subjects who were incapable of deep breathing. Oxygen consumption was measured in a valveless Sanborn machine.

CASE REPORTS

CASE 1.—A male, aged 17 years, had secondary anemia, but no organic heart disease. He showed diminished exercise tolerance. He was ambulatory, but was hospitalized for study.

CASE 2.—A female, aged 24 years, had essential hypotension but no organic heart disease. She showed normal exercise tolerance and was an apparently healthy medical student. Observations were made on two occasions by both methods under basal conditions. On the second occasion the subject had had typhoid vaccine one and one-half days earlier.

CASE 3.—A male, aged 28 years, had hypertensive heart disease and cardiac enlargement. Severe congestive failure occurred eight years ago and borderline failure has been present since then. At present he is ambulatory and is taking digitalis.

CASE 4.—A male, aged 53 years, had chronic alcoholism and cardiac enlargement. He is convalescing from an attack of acute pulmonary edema which occurred two months ago. The first attack was one year ago. He was easily breathless. He was taking no digitalis.

CASE 5.—A male, aged 55 years, had arteriosclerotic heart disease, aortic sclerosis, gastric tumor, and anemia (erythrocyte count 2,900,000). He was ambulatory, but breathless on slight effort. Hypertension with mild congestive failure occurred one year ago. The patient was hospitalized for study but was given no digitalis.

CASE 6.—A male, aged 55 years, had arteriosclerotic and hypertensive heart disease, cardiac enlargement, bundle branch block, angina pectoris, and congestive failure (onset four months ago). He is convalescing, but still bedfast and taking digitalis.

CASE 7.—A male, aged 60 years, had arteriosclerotic and hypertensive heart disease, cardiac enlargement, premature contractions, and congestive failure, onset following coronary occlusion nine months ago. He is convalescing, but still bedfast and taking digitalis.

CASE 8.—A male, aged 69 years, had arteriosclerotic and hypertensive heart disease, nephrosclerosis, and cardiac enlargement. Congestive failure at present has subsided, but patient is still bedfast and is taking digitalis.

CASE 9.—A male, aged 56 years, had anginal pain on exertion, particularly in the last year. He was ambulatory, but was hospitalized for study.

CASE 10.—A male, aged 35 years, had aortic stenosis. Onset of symptoms occurred eight years ago, with acute failure two years ago and acute pulmonary congestion 2 weeks ago. He is ambulatory after past two weeks in bed.

CASE 11.—A male, aged 70 years, had hypertensive and arteriosclerotic heart disease. He was feeble and bedfast.

CASE 12.—A male, aged 69 years, had hypertensive and arteriosclerotic heart disease and was extremely feeble and bedfast. On admission one year ago blood pressure was 154/92. He has a vegetative existence in bed, and was asleep during examination (Feb. 4, 1937).

CASE 13.—A male, aged 54 years, had hypertensive and arteriosclerotic heart disease, cardiac enlargement, and congestive failure, onset three years ago with several hospital admissions in interim. Severe orthopnea occurred. The patient died three weeks later.

CASE 14.—A male, aged 48 years, had hypertensive heart disease, cardiac enlargement, and acute pulmonary edema. He was bedfast and was taking digitalis.

CASE 15.—A male, aged 59 years, had arteriosclerotic heart disease, complete heart block, alcoholism, cirrhosis, and ascites. He was bedfast and was taking digitalis.

A source of error which is to be expected is tortuosity of the vessels. The most critical test for this factor was that on Subject 5, in whom marked tortuosity could be distinguished in the abdominal aorta by palpation, and in the thoracic aorta roentgenologically. Nonetheless, the calculated cardiac index was 2.7, as compared with a value of 2.6 by the acetylene method. (Another case of marked tortuosity was Subject 8. Here the two estimates were discrepant, but the high value obtained by acetylene, though substantiated by all three samples, is likely to have been due to excitement.) It seems probable, therefore, that the errors which are certainly present in subjects with tortuous vessels tend to cancel one another. In such subjects the pulse wave velocities must be underestimated, and the consequent errors would appear in the denominators where the values are squared. However, the volumes of these vessels, which appear in the numerators, would also be in error due to underestimates (a) in the length of the vessels and (b) in their diameter, for abnormal increases in diameter are likely to accompany tortuosity in the central vessels. If the two errors in the numerators are proportional to the tortuosity, the errors due to this factor are squared in both numerator and denominator, and are likely to cancel out.

RESULTS

Validity of the Method of Estimation by Calculation From Blood Pressure.—In Table I values are given for those subjects on whom estimates of cardiac output were made by both methods. The agreement between the two methods is fair. The mean deviation of the calculated estimate from that obtained by the acetylene method was ± 14 per cent of the latter; the average estimate by calculation was 2.35 liters/m²/min., and that by acetylene, 2.33. The mean deviation between the two methods in normal subjects has averaged ± 12 per cent. The method of calculation appears to have no new inherent errors in these cases.

In Table II the subjects are arranged in different groups, and within each group in the apparent order of their decreasing fitness.

Ambulatory Subjects.—Subject 3 had values for both the output and work of the left ventricle which were above average normal. Clinical examination likewise revealed no evidence of circulatory insufficiency at rest, although marked breathlessness occurred during physical exertion. Apparently the recorded output and work of the left ventricle were the approximate maximum obtainable, and could not be sufficiently increased to accommodate additional physiologic requirements. The estimated distensibility of the aorta appeared to equal the maximal normal values at any age.

Subject 5, like Subject 3, exhibited normal values for the output and work of the left ventricle. This was apparently attained, however, to a considerable extent by enlargement and tortuosity of the aorta.

Subject 9 had low values for distensibility of the large vessels which reflected, in this case, an advanced degree of aortic disease.

TABLE I

NO.	SEX	AGE	HEIGHT (CM.)	WEIGHT (KG.)		SURFACE AREA (SQ. M.)	OXYGEN CON- SUMPTION (ML. PER MIN.)	A-V OXYGEN DIFFERENCE (ML. PER LITER)	CARDIAC INDEX BY ACETY- LENE	CARDIAC INDEX BY CALCU- LATION	PULSE RATE	CLINICAL SYSTOLIC PRESSURE	BLOOD PRESSURES (LATERAL)
				ACTU- AL	NOR- MAL								
1	M	17	163	45.8		1.45	252	52	3.3	2.8	81	105	97/50
2	F	24	165	55.3		1.59	173	69	1.6	1.55	61	84	81/58
3	M	28	163	62.8		1.68	195	47.5	2.6	2.8	73	85	79/46
4	M	53	184	70.4		1.92	223	62	2.15	2.45	81	127	124/90
5	M	55	171	51.8	68.0	1.61	218	52	2.2	1.7	70	79	75/48
6	M	55	174	67.0		1.79	193	45	2.70	2.6	98	104	100/67
7	M	60	178	85.6	98.0	2.01	203	68	1.65	1.85	62	108	104/74
							291	69	2.05	2.3	37	169	165/66
8	M	69	175	62.2	73.0	1.75	219	44	2.9	2.05	84	122	113/86
											71	173	162/93

Average values of cardiac index were 2.35 and 2.23. Mean deviation of calculated value from acetylene value was +14 per cent.

TABLE II

OBSERVATIONS	AMBULATORY PATIENTS					OLD AGE (BEDFAST)				HYPERTENSION				CARDIAC IRREGULARITIES	
	3	5	9	10	8	11	12	13	14	15	16	17	18	19	20
Age (years)	28	55	56	35	69	70	69	54	48	59	60	60	60	60	60
Mean pulse rate	81	97	93	97	71	84	67	72	115	34	37	84	84	84	84
Clinical systolic pressure	127	104	138	92	173	216	137	201	132	156	169	122	122	122	122
Lateral pressures	124/90	100/67	135/81	89/68	169/93	212/104	127/67	197/112	128/100	109/82	147/57	165/65	113/86	113/86	113/86
Mean pressure	105	83	105	78	133	157	95	149	114	94	120	99	99	99	99
Mean pressure in systole	114	88	117	81	146	184	113	171	118	103	142	107	107	107	107
P.W.V. heart to subelav.	2.15	4.55	4.75	3.7	7.75	10.0	7.05	4.65	5.55	4.45	4.1	3.35	3.35	3.35	3.35
Subelav. to femoral	6.0	6.2	12.0	5.9	17.7	23.9	11.2	12.3	9.65	5.95	8.75	8.85	8.85	8.85	8.85
Subelav. to brachial	10.1	8.9	7.85	7.3	7.2	12.8	7.8	16.3	9.2	5.8	9.15	8.3	8.3	8.3	8.3
Femoral to dorsalis	10.25	9.7		8.0	9.8	15.75	11.8	17.2	26.1	12.55	9.35	7.3	7.3	7.3	7.3
Effect of distension of aorta	0.96	0.55	0.38	0.50	0.15	0.08	0.22	0.34	0.34	0.49	0.55	0.76	0.76	0.76	0.76
Effect of distension of peripheral artery	0.08	0.11		0.13	0.11	0.04	0.08	0.03	0.03	0.09	0.11	0.17	0.17	0.17	0.17
Cardiac index	2.45	2.35	(2.50)	2.05	2.05	1.3	1.2	2.25	1.30	1.8	2.50	2.15	2.15	2.15	2.15
Stroke vol./sq. m.	30	24	27	21	29	15	18	31	12	53	68	26	26	26	26
Effect of peripheral resistance	127	105	(126)	78	196	362	238	200	212	153	144	137	137	137	137
Duration of Q-T (elect. systole)	0.339		0.377	0.320	0.387	0.335	0.348	0.470	0.365	0.500	0.396	0.404	0.404	0.404	0.404
Duration of mech. systole*	0.336	0.302	0.372	0.330	0.355	0.275	0.308	0.305	0.251	0.422	0.340	0.342	0.342	0.342	0.342
Compress. work lt. vent/beat/sq. m.	4,730	3,030	3,840	>2,100	5,700	3,320	2,800	6,250	1,560	7,440	13,100	3,730	3,730	3,730	3,730
Compress. work lt. vent/min./sq. m.	3.85	2.95	3.55	>2.05	4.1	2.8	1.8	4.5	1.65	2.95	4.85	3.15	3.15	3.15	3.15

Attention is drawn by italics to the data considered of greater significance.

*Measured from the start of rising tension time to the second sound.

Subject 10, whose clinical examination revealed aortic stenosis, had a relatively low cardiac output in spite of a probably high work level of the heart. (An accurate estimation of the work of the heart could not be obtained in the presence of the valvular lesion.) The peripheral vascular system appeared normal.

Hypertensive Subjects of the Old-Age Group.—The three, elderly, hypertensive subjects (8, 11, and 12), who were bedfast, formed a strong contrast with the ambulatory group. In all cases the effective distensibility of the aorta was low. The effective distensibility of the more peripheral vessels did not appear particularly low (except in Subject 11), but these values may have resulted from underestimation of the pulse wave velocity due to tortuosity of the arteries.

The effective peripheral resistances were high. The cardiac output was low in Subjects 11 and 12. In Subject 8 the cardiac index was 2.05, but this value was likewise low when considered in relation to the increased work of the left ventricle. The low cardiac output can probably be correlated with the extremely feeble and apathetic condition of these patients.

The blood pressure in Subjects 8 and 11 was high. In Subject 12 the blood pressure was normal, but hypertension was nevertheless an etiologic factor. This case illustrates how hypertension can be masked by a low cardiac output, although the distensibility of the aorta is subnormal and the peripheral resistance is high.

Subject 12 suffered from frequent attacks of paroxysmal nocturnal dyspnea. A possible cause for these attacks was demonstrated when the patient fell asleep during a repetition of his examination. Sleep was accompanied by marked slowing of the heart rate. The already low cardiac output thereupon sustained a further decrease, until the cardiac index was only 1.15.

Hypertension in the Middle-Aged Group.—The data on these subjects show certain quantitative differences from those in the previous group. Reduction in distensibility was found chiefly in the peripheral arteries, and was relatively less pronounced in the aorta. The cardiac output was very low in Subjects 14 and 15, and this could be correlated with the more severe symptoms of these patients, as compared with Subject 13, who had a normal cardiac output. Subject 13, however, was the only patient who died within three weeks of his examination. His higher level of cardiac work, by exerting an excessive strain on the heart, may have been more harmful than the low cardiac outputs of the other two distressed, but still living, subjects.

Cardiac Irregularities.—Subject 15 had complete heart block. The slow heart rate resulted in a large stroke volume and a high level of cardiac work per minute.

Subject 7 had ventricular premature contractions which produced a very irregular pulse rate, with periods in which the rate was 37 (due

to pulse deficit), other periods in which it was 84, and still others in which it alternated rapidly between the two levels. The values observed under the two main conditions are shown in Table II. Estimates of the cardiac output were probably not much in error, for they gave a cardiac index of 2.3, whereas the acetylene method gave one of 2.05.

A series of pulse curves illustrating the shift from the slow pulse, when extrasystoles were present, to the rapid pulse, when extrasystoles were absent, is reproduced in Fig. 1, together with simultaneous electrocardiograms.

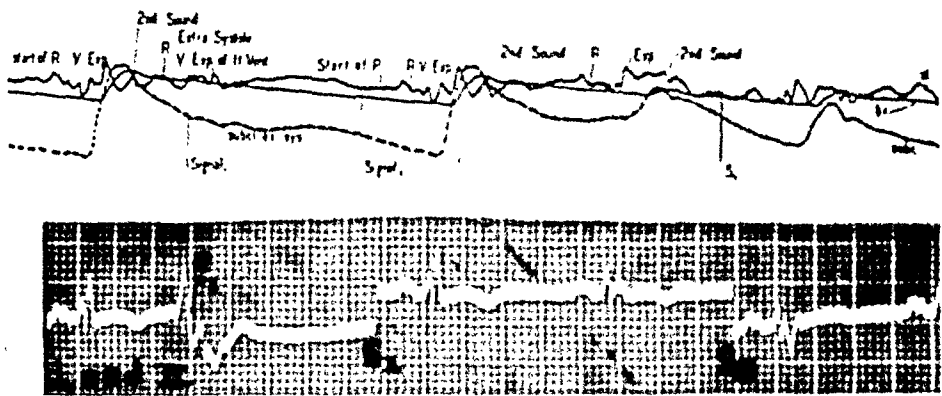


Fig. 1.—Records of sternal pulsation and subclavian (dotted line) and brachial pulses of Subject 9 during the change from the slow pulse to the fast pulse, redrawn and reduced (about $\frac{1}{2}$) to the same time relations as the electrocardiogram which was taken simultaneously. The latter is shown below. Corresponding points on the two records are indicated as signals S_1 , S_2 , and S_3 ; at these points the electrocardiogram is changed in level. Pulse 2 is of ventricular origin; it is not preceded by a P wave. The later pulses at the faster pulse rate are noteworthy for very long and abnormal QRS complexes. The pressure levels of the two types of pulse are indicated in Table II; the intervals between the start of R and the subclavian pulse are indicated in Table III.

TABLE III

TYPE OF PULSE	DURATION OF QRS (SEC.)	START OF R TO SUBCLAVIAN (SEC.)	START OF R TO START OF CONTRACTION (SEC.)	RISE IN TENSION TIME (SEC.)	START OF EJECTION TO SUBCLAVIAN PULSE (SEC.)
Large slow beats	0.099	0.135	0.022	0.062	0.051
Small fast beats	0.154	0.206	0.023	0.121	0.062
Premature contractions	0.230	0.275	0.042	0.190	0.043

The sequence of events may be followed from these records and the data in Table III. With the slow pulse and the long rest between normal beats, conduction was fairly adequately accomplished, and the QRS complex was not very abnormal. The stroke volume and the cardiac work were very high. The change to a more rapid pulse, without extrasystoles, lessened the load as far as heart work was concerned, but left little time for recovery of the conducting tissue; the QRS complex became grossly lengthened and abnormal in shape. The time relations

allowed the conclusion to be drawn that the delayed conduction, on which the abnormal complex depended, was affecting the left ventricle, and also that the origin of the premature beats was in the right ventricle.

The time relations which were observed merit brief discussion. The faster pulse beats, as well as the premature contractions, were associated with a much increased duration of the QRS complex, and also with a great exaggeration of the interval between the start of the R wave and the subclavian pulse. The increases in these two intervals were approximately of the same order, and not open to question. Although the sternal pulsations were *interpreted* as indicating an abnormally long period of rising tension time in the left ventricle, such deductions were not essential to the argument. There was unquestionable evidence of asynchronism of the two ventricles. The auricular contractions were also often abnormal or not synchronized, for the P wave was commonly notched or double (Fig. 1); accompanying the double P wave there was a duplication of the auricular wave in the sternal pulsation.

DISCUSSION

The data presented give evidence that the method of estimating cardiac output from blood pressure measurements can be applied without serious errors to patients with cardiovascular disease other than aortic incompetence.⁵ It is probable that it would be inapplicable to patients with aneurysms, although this has not been investigated.

Calculation of the work of the left ventricle demonstrated that the additional work which was required in order to maintain the cardiac output could not be accomplished without a considerable increase in the oxygen consumption of the heart. If the oxygen is supplied to the heart at a normal tension, there must also be a considerable increase in the coronary flow. Such data are in agreement with Rasmussen's⁷ demonstration that there is an increased oxygen usage in hypertensive subjects. If the oxygen intake and cardiac output are normal or subnormal in such patients, one must assume that this increased utilization by the heart is accompanied by a considerable deficiency in the supply of blood and oxygen to the peripheral tissues.

Cardiac indices of the same order as those here reported were found by Grollman, et al.,⁸ in cases of congestive failure. The average in their eight cases was 1.87, with extremes of 1.29 and 2.25; the average of the values obtained by calculation in the eleven cases of congestive failure here described was 1.72, with extremes of 1.15 and 2.25. The higher cardiac outputs observed in this series occurred in patients who appeared capable of maintaining a relatively high grade of mental or physical activity. Such activity may, however, be attainable only at the expense of an excessive load on the heart (Subject 13). A low cardiac output may be associated with evidence of considerable damage to the peripheral vascular system (Subject 14), or with low activity and a vegetative existence, with no indication of any progressive development of symptoms of congestive failure (Subject 12). In such cases the work performed by the heart may be markedly subnormal.

Analysis of the type which we have described enables one to recognize hypertension in subjects who have no hypertension (either systolic or diastolic) at the time of examination (Subjects 12 and 14). Comparison of the middle-age and old-age groups gives some indication that the method might distinguish between hypertensive subjects of different types. Analysis of irregular heart action, with pulses at various pressure levels, can be attained, and affords evidence as to which side of the heart is affected mainly by deficient ventricular conduction, as well as to the site of origin of premature ventricular contractions. The principles discussed by Katz, et al.,⁹ and by Braun-Menendez and Solari¹⁰ are applicable to the records obtained.

CONCLUSIONS

1. It is shown that the stroke volume of the heart may be calculated from measurements of pulse pressure and pulse wave velocity on patients with various types of cardiovascular disease (except aortic regurgitation) without apparent, serious error.

2. The applicability of the method to subjects with tortuous vessels (which would appear likely to introduce serious errors) is attributed to the introduction of errors of approximately uniform extent in both the numerators and denominators of the equations.

3. The method is utilized to calculate the work of the left ventricle. In cases of hypertension in which the cardiac output is well maintained, the work which the heart has to perform is shown to be high. It is demonstrated that, unless this work is performed under very unfavorable circumstances, it must be accompanied by an increased oxygen intake by the subject and by an increased coronary circulation. A normal oxygen intake and a normal cardiac index in such patients do not, therefore, indicate a normal and adequate supply of oxygen and blood to the peripheral tissues.

4. Attention is drawn to the development of decreased distensibility of the large vessels in two groups of patients, namely, an older group with the changes mainly in the aorta, and a middle-age group with the changes mainly in the peripheral arteries.

5. It is shown that hypertension in cases in which there is temporarily no hypertension, because of a low cardiac output, may be recognized by such analysis, even when the blood pressure is normal.

We should like to take this opportunity to thank the staff of the Philadelphia General Hospital and, in particular, Dr. William E. Robertson, whose cooperation made this work possible. Our thanks are also due to the Faculty Research Committee of the University of Pennsylvania for financial assistance in this research.

REFERENCES

1. Bazett, H. C., Cotton, F. S., Laplace, L. B., and Scott, J. C.: The Calculation of Cardiac Output and Effective Peripheral Resistance From Blood Pressure Measurements With an Appendix on the Size of the Aorta in Man, *Am. J. Physiol.* 113: 312, 1935.

2. Bazett, H. C., Scott, J. C., Maxfield, M. E., and Blithe, M. D.: Calculation of Cardiac Output From Blood Pressure Measurements Before and After Meals, *Am. J. Physiol.* 116: 551, 1936.
3. Bazett, H. C., Scott, J. C., Maxfield, M. E., and Blithe, M. D.: Effect of Baths at Different Temperatures on Oxygen Exchange and on the Circulation, *Am. J. Physiol.* 119: 93, 1937.
4. Scott, J. C., Bazett, H. C., and Mackie, G. C.: Climatic Effects on Cardiac Output and the Circulation in Man, *Am. J. Physiol.* 129: 102, 1940.
5. Bazett, H. C., Laplace, L. B., and Scott, J. C.: *AM. HEART J.* 22: 749, 1941.
6. (a) Bazett, H. C.: Analysis of the Time Relations of Electrocardiograms, *Heart* 7: 353, 1920.
(b) Bazett, H. C., and Sands, J.: The Significance of Measurements of the Duration of Systole, *Ann. Clin. Med.* 5: 190, 1926.
7. Rasmussen, H.: Über den Grundumsatz bei essentieller Hypertonie, *Acta med. Scandinav.* 93: 594, 1938.
8. Grollman, A., Friedman, B., Clark, G., and Harrison, T. R.: XXIII. Studies in Congestive Heart Failure. A Critical Study of Methods for Determining the Cardiac Output in Patients With Cardiac Disease, *J. Clin. Investigation* 12: 751, 1933.
9. Katz, L. N., Landt, H., and Bohning, A.: Delay in Onset of Ejection of Left Ventricle in Bundle Branch Block, *AM. HEART J.* 10: 681, 1935.
10. Braun-Mendendez, E., and Solari, L. A.: Ventricular Asynchronism in Bundle Branch Block, *Arch. Int. Med.* 63: 830, 1939.

THE ESTIMATION OF CARDIAC OUTPUT FROM BLOOD PRESSURE AND PULSE WAVE VELOCITY MEASUREMENTS ON SUBJECTS WITH CARDIOVASCULAR DISEASE

II. AORTIC REGURGITATION

H. C. BAZETT, M.D., L. B. LAPLACE, M.D., AND J. C. SCOTT, PH.D.
PHILADELPHIA, PA.

IN PART I of this report,¹ it was shown that the method of calculating the stroke volume of the heart from measurements of pulse pressure and pulse wave velocity² is applicable to patients with various types of cardiovascular disease other than aortic regurgitation. The method is not applicable to patients with aortic regurgitation because the pulse pressure is determined by the volume of blood which returns to the left ventricle, in addition to that which proceeds through the aorta. The values obtained, therefore, do not represent the effective stroke volume.

If the cardiac output in a patient with aortic regurgitation is measured by the acetylene method, a comparison of the values so obtained with those obtained by somewhat modified calculations from the pulse pressure supplies an estimate of the degree of regurgitation. This, in turn, permits investigation of the nature and extent of the physiologic handicap which aortic regurgitation imposes upon the heart. The observations to be reported are concerned with the results of this procedure as applied to two subjects.

METHODS

The procedure used in estimating the cardiac output by the acetylene method, as well as the technique employed in obtaining the data used in the equations, was the same as that already described.¹

The method of calculation² required certain changes, for the outflow from the aorta in diastole occurs both into the smaller vessels and, by regurgitation, into the ventricle, whereas in systole it occurs only into the vessels. The following modification was used:

The calculation is made in the ordinary way from the fall of pressure in diastole. This gives the blood leaving the aorta for the capillaries (V_a), and also the regurgitating blood (x).

$$(4) \quad V_a + x = \frac{12.7 (Z-D)}{100} \frac{V_1}{v_1^2} + \frac{V_2}{v_2^2} + \frac{V_3}{v_3^2} + \frac{V_4}{v_4^2}$$

From the Departments of Physiology of the University of Pennsylvania and Hahnemann Medical College, and from the Philadelphia General Hospital.
Received for publication April 2, 1941.

V_d and x cannot be distinguished. Equations (2) and (3), which were given in Part I,¹ may be combined as follows:

$$(5) \quad \frac{V}{V_d} = 1 + \frac{s}{d} \frac{(Ms - 20)}{(Md - 20)}$$

If V be determined by the acetylene method, V_d may be calculated by equation (5). If V_d be subtracted from the value determined by equation (4), the value of x is obtained.

Two subjects who had aortic regurgitation were studied.

CASE 1.—A male, aged 40 years, had syphilitic heart disease. The heart was greatly enlarged; rhythm was normal. He had angina pectoris and had had congestive failure, onset two years previously, with several hospital admissions in the interim. He was confined to bed and digitalized.

CASE 2.—A male, aged 26 years, had rheumatic heart disease. There was extreme cardiac enlargement. Rhythm was normal. The patient had no symptoms of cardiac insufficiency and played basketball without discomfort. No medication was administered.

Subject 1 was studied two hours after a light breakfast; Subject 2, under basal conditions.

RESULTS

A summary of the values obtained on the two subjects is included in Table I.

In Subject 1, the effective stroke volume by the acetylene method (somewhat doubtful because of difficulties in breathing) was 67.4 ml.; the true V_d was 28.9 ml., and x was 13.4 ml. Apparently, therefore, there was with each contraction of the left ventricle an expulsion of 80.8 ml., of which 13.4, or 16.6 per cent, regurgitated during diastole. The distensibilities of the large vessels were subnormal, i.e., 0.36 ml./m²/mm. Hg for the two central sections, and 0.10 for the two more peripheral. (The normal values for these distensibilities in subjects up to 40 years of age are about 0.52 and 0.14.) The blood pressures were high, and the work of the left ventricle was therefore much increased as the result of all these factors, in spite of the moderate degree of regurgitation. The compression work was calculated as 16,000 Gm. cm. per beat, and as 11.8 kilogram meters per minute, as compared with normal levels of about 6,900 (4,150 per square meter) and 4.85 (2.9 per square meter). The extra work would necessitate the use of an additional 17 ml. of oxygen per minute (assuming a mechanical efficiency of 1 to 5) and an additional coronary flow of some 300 ml. per minute (assuming an oxygen utilization of 55 ml. per liter). The actual increases should be greater, for any increase in basal metabolism would require, also, an increased flow through the skin for heat loss. If the mechanical efficiency of the heart were lowered by myocardial changes, the increase in metabolism would also have to be greater. Consequently, a normal cardiac index is

TABLE I

SUB- JECT NO.	SEX	AGE (YR.)	HEIGHT (CM.)	WEIGHT (KG.)		SURFACE AREA (SQ. M.)	OXYGEN CONSUMPTION PER MINUTE (ML.)	ARTERIO- VENOUS OXY- GEN DIFFER- ENCE (ML. PER LITER)	CARDIAC INDEX BY ACETYLENE	CARDIAC INDEX BY CALCULA- TION (UNAD- JUSTED)	PULSE RATE	CLINICAL SYSTOLIC PRESSURE	ESTIMATED LATERAL BLOOD PRESSURES
				ACTUAL	NORMAL								
1	M	40	166	61.2	73.0	1.66	246	48.5	3.0	4.4*	74.0	181	172/72
2	M	26	178	76.8		1.95	337	46.8 56.5	3.7 3.05	8.05*	69.3	164	151/49

*The cardiac outputs here given are those calculable by the method as if no aortic lesion were present. The gross exaggeration that results is obvious. For calculation of the amount regurgitated see text.

not to be anticipated in such cases, and, even if it were normal, it would not indicate a normal peripheral circulation.

In Subject 2, the values were even more striking. This subject was relatively fit (playing college basketball), and had an enormous heart. An orthodiagram showed that the transverse diameter of the heart was 17.5 cm. in a thorax 26.1 cm. in diameter.

At the time when the observations were made, the subject was somewhat excited, and the acetylene procedure was consequently carried out twice, before and after obtaining blood pressure records. The pulse rate was at first 74 to 78, later, 52 to 67. The diastolic pressures indicated in Table I appear high as compared with the auscultatory estimates usually used in such cases. The diastolic pressure was not measurable in this subject by auscultation; the apparent level was zero.

If the mean values for cardiac output (6.57 liters) and for pulse rate (69.3) are used, the real stroke volume is calculated as 96.2 ml. From the blood pressure data a regurgitation of 41.7 ml. is estimated. The left ventricle therefore ejected 137.9 ml., of which 31 per cent regurgitated. The distensibility of the vessels was high, namely, 0.56 ml./mm. Hg/m² for the central, and 0.23 for the peripheral, vessels. The high degree of regurgitation and the high systolic pressure gave high estimates for the compression work of the left ventricle, namely, 23,000 Gm. cm./beat and 16.0 kilogram meters/min., as compared with normal values for a subject of this size of about 8,100 and 5.6, respectively. The large amount of blood expelled in systole also implied a high mean velocity in the aorta of about 138.5 cm./sec., so that the work of developing kinetic energy must have been also quite high. This work may be calculated on the assumption of a uniform velocity of expulsion, and the actual work is, on such a calculation, certainly underestimated. It may also be calculated on an assumption of a constant rate of shortening of circular fibers surrounding a spherical ventricle. Assuming a final internal diameter of 2 cm. for the "emptied" left ventricle, one may calculate an initial diameter of 6.5 cm. The cross-section area of the aorta was assumed to be 2.77 cm.² and the duration of ejection was 0.36 sec. Calculation of the work involved in producing kinetic energy was 1,425 Gm. cm./beat on the assumption of a constant velocity of ejection, and 2,875 on that of a constant rate of muscular shortening. The real value probably lies between these two estimates.

The increased work of production of kinetic energy above a probable normal level on the two assumptions was 1,260 Gm. cm. per beat on the first, and 2,600 on the second. The total work of the left ventricle may be calculated as exceeding the normal by 675 to 732 kilogram meters per hour. If the same assumptions are made as for Subject 1, an additional oxygen consumption of 27 to 30 ml. per minute must be expected, which should give a total basal oxygen consumption of 296 to 299 ml. The observed value at the time of examination was 337, and, on

the next morning, when the subject was more relaxed, 286. The increased coronary flow to be anticipated would be 500 to 550 ml./minute. The data indicate that, whereas under normal basal conditions the heart is likely to consume 8 to 9 per cent of the total oxygen utilized, this proportion may be readily doubled when the heart is abnormal.

Other approximate calculations may be made on Subject 2. The work of inducing kinetic energy in the left ventricle was 5.8 to 10.7 per cent of the total work of this ventricle (according to the assumptions adopted), as compared with 2.0 to 3.3 on similar assumptions for a normal subject. The difference would be much greater under nonbasal conditions. If normal pressures be assumed for the pulmonary artery, the relative work of the two ventricles may be calculated. Whereas in the normal subject the work of the left ventricle is about twice that of the right, in Subject 2 the ratio was about 3:1. This may be compared with the relative weights of the ventricles in such cases. Lewis³ reported a normal ratio for LV/RV of 1.81, and ratios as high as 2.74 and 3.44 in cases of aortic regurgitation of an extreme degree.

SUMMARY AND CONCLUSIONS

In patients with aortic regurgitation, the degree of regurgitation may be estimated from the difference between values for cardiac output made by the acetylene method and a modification of the method of calculation from pulse pressure and pulse wave velocity. By this procedure, the regurgitation was found in two subjects to amount to 13.4 and 41.7 ml., respectively.

From data obtained in this study, it appears that the presence of free aortic regurgitation may double the oxygen utilization of the heart, and require an increase of over 500 ml. per minute in the coronary blood flow. The work of the left ventricle may be increased by approximately 50 per cent or more.

REFERENCES

1. Bazett, H. C., Laplace, L. B., and Scott, J. C.: The Estimation of Cardiac Output From Blood Pressure and Pulse Wave Velocity Measurements on Subjects With Cardiovascular Disease. I. Cardiovascular Disease Other Than Aortic Regurgitation, *AM. HEART J.* 22: 737, 1941.
2. Bazett, H. C., Cotton, F. S., Laplace, L. B., and Scott, J. C.: The Calculation of Cardiac Output and Effective Peripheral Resistance From Blood Pressure Measurements With an Appendix on the Size of the Aorta in Man, *Am. J. Physiol.* 113: 312, 1935.
3. Lewis, T.: Observations Upon Ventricular Hypertrophy With Special Reference to Preponderance of One or Other Chamber, *Heart* 5: 367, 1914.

A RECORD CASE OF THE TETRALOGY OF FALLOT, WITH COMMENTS ON METABOLIC AND PATHOLOGIC STUDIES

JOHN H. TALBOTT, M.D., FREDERICK S. COOMBS, M.D.,
BENJAMIN CASTLEMAN, M.D., FRANCIS L. CHAMBERLAIN, M.D.,
W. V. CONSOLAZIO, B.S., AND PAUL D. WHITE, M.D.
BOSTON, MASS.

FOR more than a decade, anoxemia has been of special interest in certain of the laboratories from which this report originates. The first and probably the only D'Oeagne nomogram ever constructed of the acid-base balance of the blood of a patient with congenital heart disease and cyanosis was based upon data collected at the Massachusetts General Hospital in 1925.¹ Subsequent communications have been concerned with the effect of (a) a diminished oxygen percentage on normal subjects at sea level,² (b) a diminished partial pressure of oxygen on temporary residents in the Colorado Rockies at 10,000 and 14,000 feet,³ (c) a diminished partial pressure of oxygen on temporary residents in the Chilean Andes at altitudes as high as 20,100 feet,⁴ and (d) a diminished partial pressure of oxygen on permanent residents in the Andes.⁵ The unsaturation of arterial blood with oxygen and a diminished transport of oxygen to the tissues were the common denominator in all of the studies.

Because of the desire to enhance our knowledge of the effects of prolonged anoxemia at a barometric pressure corresponding to sea level conditions, we have collected extensive metabolic data on a patient who suffered from cyanotic congenital heart disease for nearly twenty years. A comprehensive post-mortem examination confirmed the clinical diagnosis of tetralogy of Fallot. The patient was seen in our hospital for the first time at the age of 18, and stated that his lips had been blue since the age of 2. He was an intelligent, cooperative, and, at that time, ambulatory patient, and agreed to participate in a metabolic experiment. He was transferred, therefore, to the research ward and remained for approximately a month. He was readmitted to the hospital on three occasions. At all times he was under the medical supervision of members of the medical and cardiac clinics. Subacute bacterial endocarditis was suspected at various times, but the blood cultures invariably were

This study was aided in part by a grant from the Corn Industries Research Foundation.

From the Medical Clinic, the Medical Laboratories, and the Laboratory of Pathology of the Massachusetts General Hospital, and from the Fatigue Laboratory, Harvard University, Boston.

Received for publication April 7, 1941.

reported as showing no growth. Terminally, the patient suffered from a large cerebral abscess. Detailed acid-base studies with other metabolic data on a patient with congenital heart disease are not often available. These observations, together with a post-mortem report, permit one to designate the complete study as unique.

REPORT OF CASE

D. B., Massachusetts General Hospital Unit No. 91316, a Grecian-born school boy, aged 18 years, was admitted to the Massachusetts General Hospital on Nov. 5, 1937, complaining of dyspnea, orthopnea, a dry cough, and weakness for three weeks.

Family History.—His father, mother, sister, and brother were living and well. Congenital, hereditary, and cardiac stigmas were denied.

Past History and Present Illness.—The patient was apparently normal and well until he was stricken with diphtheria at the age of 2. Careful questioning of the parents failed to elicit any history of cyanosis prior to this illness. After the attack of diphtheria his lips became blue and remained blue during the following seventeen years. For several years prior to the hospital admission his parents believed that he had been more cyanotic than immediately before admission. Between the ages of 2 and 5 he suffered from sudden attacks of syncope. Thereafter he was free from them, and entered school, where he progressed without difficulty until the age of 9. At that time he had a severe attack of tonsillitis. This was followed by swelling of the ankles and knees. He maintained that he was paralyzed during this illness, but it is more likely that he was incapacitated by rheumatic polyarthritis. Recovery was slow, but eventually he was able to return to school with no residual joint dysfunction. His physical activity was curtailed, however, and the strenuous sports engaged in by boys of his age were forbidden.

Each winter he suffered from one or more attacks of tonsillitis, with little or no fever or other constitutional symptoms. His voice became "adenoid" in quality, and he was able to breath only through his mouth. There was recurrent swelling of his ankles during the day, and they became tender when he was fatigued. Frequency of urination during the day and enuresis at night were troublesome. He carried on his school work without difficulty, and maintained a scholastic standing near the top of his class. Three years before admission he had an acute, left middle-ear infection which was followed by a purulent discharge. The discharge recurred frequently, and loss of acuity of hearing eventually developed. He also had, two or three times a year, sudden attacks of earache, severe dizziness, and vomiting, and would fall to the ground. Five weeks before admission, after climbing the stairs to his classroom, he experienced acute dyspnea, became weak, and for several minutes was partially apneic. After an attack of unproductive coughing he felt somewhat better; he had a frontal headache, but continued with his school program. Three days before admission the dyspnea became unbearable; he was compelled to remain at home, and finally decided to enter the hospital.

Physical Examination.—Examination showed that the patient was moderately well developed, but rather poorly nourished. There was general cyanosis, which was most marked in the lips and nails, but was also evident in the skin over the entire body. The ocular fundi showed hazy disc margins; the veins were markedly dilated, whereas in the periphery the arteries were narrow. No retinal exudates or hemorrhages were seen. The sinuses were dark on transillumination. Both nares showed considerable crusting. The tonsils were hypertrophied and showed evidence of chronic infection. Both aural canals contained foul-smelling, thick pus. The drums

had been destroyed. The hearing was slightly impaired. There was a left dorsal scoliosis, with a right dorsal lumbar curve, and moderate kyphosis was present. The chest was barrel-shaped. There was a precordial bulge. Many dilated veins were visible. Examination of the heart by Dr. Edward Bland was reported as follows: "The heart showed well-marked enlargement, with prominent systolic pulsations to the right as well as to the left of the sternum. No thrill was palpable. On auscultation there were (1) prolongation and reduplication of the first sound over the lower cardiac area, and (2) a moderately loud and long, early, diastolic murmur which was widely transmitted, but was best heard along the left sternal border. There was a slight systolic blow at the apex. The pulmonary second sound was present, but was not remarkable. Fluoroscopic examination showed (1) well-marked cardiac enlargement, with the general configuration of right ventricular hypertrophy, (2) a full-sized, dynamically pulsating aorta, and (3) absence of unusual prominence of the pulmonary conus, and normal hilus shadows without a hilus dance. In the right anterior oblique view there was but slight encroachment on the posterior mediastinal window." The blood pressure was 116/84 in the arm and 120/84 in the leg. Examination of the abdomen was negative.

There was marked soft tissue clubbing of the fingers and toes. The knees showed soft tissue swelling and were tender on palpation. There was no limitation of motion. There was slight edema of the shins and ankles. There were marked tortuosity and engorgement of the leg veins.

Partial Laboratory Data.—The hemoglobin measured 140 per cent by the Sahli method; the erythrocyte count was 8,660,000; and the leucocyte count was 5,900. No satisfactory blood smear or differential count of the leucocytes was obtained because of the great number of erythrocytes. The Hinton reaction on the blood was negative. The basal metabolic rate on two occasions was +1 and +5 per cent, respectively. The vital capacity was 2.6 liters.

Casual specimens of urine showed a maximum specific gravity of 1.018 and a trace of albumin, but no sugar or diacetic acid. Examination of the centrifuged specimen showed several erythrocytes, a few leucocytes, and occasional hyalin and granular casts. A urine concentration test after abstinence from fluid for twelve hours showed a maximum specific gravity of 1.018. This value is corrected for the protein which was present. The excretion of phenolsulphonphthalein, injected intravenously, was 20 per cent in fifteen minutes, and totaled 30 per cent in one hour. Two blood cultures were negative for pathogenic organisms.

The venous pressure* was 80 mm. of water by the Moritz and Tabora method. Measurement of the circulation time following the intravenous injection of 10 c.c. of decholin gave discordant results and a doubtful end point. At the first determination the end points were thirty-five and fifty-six seconds, respectively (normal, ten to sixteen seconds). At the second, they were twenty-six and thirty-four seconds, respectively. The respiratory minute volume was 7.7 liters. The oxygen consumption per minute was 244 c.c., and the respiratory quotient was 0.85.

The electrocardiogram showed marked right axis deviation, unusually large P waves, and a P-R interval of 0.20 second.

Röntgenologic Examination.—The following interpretations were reported by Dr. A. O. Hampton: "There is marked thickening of the mucous membranes of both antra. There may be a small amount of fluid on the left side. The ethmoids show some thickening of the mucous membranes. The frontal sinuses are underdeveloped. There is sclerosis of both mastoids. The heart is grossly enlarged and rounded in shape. The greatest enlargement appears to be in the region of the auricles and the right ventricle. The pulmonary conus and pulmonary vessels are

*We are indebted to Dr. C. Sidney Burwell for the measurements described in this paragraph.

relatively small. The shadow of the superior vena cava appears large. The size of the aorta is greater than normal. Both auricles are dilated in the oblique view. Appearance is that of congenital heart disease of a rather unusual type. The most unusual features are enlargement of the aorta and absence of dilatation of the pulmonary vessels. An intravenous pyelogram shows the kidney outlines to be considerably larger than normal and smooth in outline. The dye is excreted poorly. The kidney pelves and calices are not distinctly seen; they are small and show a suggestion of multiple pressure defects. The appearance is similar to that of polycystic kidneys. The phalanges of the hands and feet are long and tapering, especially the terminal portions. There is no bony clubbing and no periosteal reaction. There is some thickening of the terminal soft tissues. "The structure of the bones appears normal."

Subsequent Course.—The patient was readmitted to the hospital three times during the following year. A diminishing cardiac reserve was responsible for the second admission, on Feb. 16, 1938. The blood pressure was 100/65. A blood culture was negative. He was discharged as somewhat improved.

The third admission, March 15, 1938, was necessary because of an acute enteritis. The cardiac state was thought to be unchanged at that time. Several urine specimens showed erythrocytes and leucocytes, albumin, and a few granular and hyalin casts. The leucocyte count varied between 4,000 and 6,700. Two stools showed a positive guaiac test, and three, a negative. Three blood cultures were negative. A tentative diagnosis of subacute bacterial endocarditis was based upon the following evidence: cardiac disease, hematuria, fever, pleural pain (from pulmonary embolism?), and possible mesenteric thrombosis.

The fourth admission, Nov. 14, 1938, was five days before death. A greater part of the intervening time had been spent in bed, but in moderate comfort. At one time, pains in the elbows, wrists, and knees were distressing. It was undecided whether this was caused by acute rheumatic fever or pulmonary osteoarthropathy. There were two attacks of chest pain which were thought to have been associated with pulmonary infarcts. Five days before admission a severe headache developed. This was largely responsible for his return to the hospital.

Physical Examination.—The pulse rate was 80 per minute, and the pulse was regular. The blood pressure was 110/70. The heart examination was as described on the first admission. The lungs were clear and resonant. The edge of the liver was felt 3 cm. below the costal margin, and was slightly tender. The spleen was not felt. The ankles were moderately swollen. Weakness of the left side of the face and body was apparent. This, together with severe temporal headache, suggested a cerebral abscess. Coma supervened two days before death.

Laboratory Studies.—The leucocyte count varied between 3,900 and 7,200. The urine analyses and electrocardiogram were unchanged. A lumbar puncture showed 312 polymorphonuclear cells, 88 lymphocytes, and 70 erythrocytes per cubic millimeter. The concentration of total protein was 25 mg. per 100 c.c., of sugar, 74 mg. per 100 c.c., and of chloride, 721 mg. per 100 c.c. The gold sol curve was 0000121000. Cultures of three samples of spinal fluid and two samples of blood were negative. A culture from the throat and one from the ear showed no growth of pathogenic organisms. An arterial blood sample was obtained four hours before death. An electrocardiogram three hours before death was interpreted as follows: "Marked sinus arrhythmia, rate 55. In Lead III, two instances of ventricular escape are seen, with blocked P waves subsequently. The P-R interval equals 0.22 second. Marked right axis deviation. T₁ upright, T₂ inverted, and T₃ inverted. Prominent U waves."

The autopsy was performed three hours after death.

POST-MORTEM EXAMINATION

The post-mortem examination showed a markedly cyanotic, barrel-chested boy, with marked clubbing of the fingers and toes. The blood vessels of the skin were prominent, and appeared as a network of deep purple lines; indeed, all the blood vessels throughout the body were extremely prominent.

Heart.—The heart was markedly enlarged, and weighed 600 Gm. Most of the enlargement was due to the enormous hypertrophy of the right ventricle, which comprised roughly two-thirds of the total volume of the heart. The right ventricular wall measured 17 mm. in thickness. The left ventricle was relatively small, and its wall measured 14 mm. The right auricle was dilated and much more prominent than the left. The wall of the right auricle measured 2 to 3 mm. in thickness, and that of the left measured 1.5 to 2 mm. in thickness.



Fig. 1.—Exposure of right ventricle, with probe inserted through the stenotic and calcified pulmonary valve.

The congenital abnormalities were numerous. There was complete transposition of the aorta, which came directly from the right ventricle. The wall of the aorta was slightly thicker than normal, and measured 2 to 3 mm.; otherwise it was negative. The ductus arteriosus was completely closed, and there was just a dimple on the aortic intima. There was a large interauricular septal defect which measured 6 cm. in circumference. Just below the aortic valve there was a large inter-ventricular defect which measured 5 cm. in circumference. This opened into the

left ventricular cavity just below the pulmonary valve. The pulmonary valve was bicuspid, with two well-defined commissures. The diagonal distance between the two commissures from their points of attachment on the pulmonary artery was 2.5 cm. The valve cusps were thickened, fibrous, and fused along most of this distance, except at the central portion, where an opening not more than 2 to 3 mm. in diameter was present (Fig. 1). Attached to one edge of the valve margin, undoubtedly adding to the stenosis, was a somewhat granular and calcified vegetation which measured 6 mm. in diameter and 15 mm. in length. The pulmonary artery was narrow and markedly thinned, and measured not more than 0.3 mm. in thickness. Just above the valve there was an intimal erosion about 1 cm. in diameter which was produced unquestionably by the constant irritation of the calcified vegetation. The aortic valve measured 8 cm. in circumference, and the



Fig. 2.—Exposure of the chambers of the heart, showing shortening and thickening of the chordae tendineae of the tricuspid valve.

cusps showed slight interadherence at their commissures. In addition, there were a few, pinkish-gray, firm, nodular vegetations, measuring 1 to 4 mm. in diameter, along the line of closure of the valve cusp. The tricuspid valve (Fig. 2) measured 11 cm. in circumference and showed slight, but definite, shortening and thickening of the chordae tendineae. Along the line of closure there were numerous, pale-yellow vegetations which were as large as 5 mm. in diameter. The mitral valve measured 9 cm., and was negative. The coronary arteries were patent throughout. Microscopic examination of the myocardium showed numerous small foci of fibrosis and lymphocytic infiltration, but no lesions suggestive of Aschoff nodules could be identified. The microscopic section of the tricuspid valve showed a degree of fibrosis and increased vascularity which was consistent with rheumatic infection. The pulmonary valve was too fibrotic and calcified to allow an accurate opinion regarding previous rheumatic involvement.

Lungs.—Both lungs were uniformly well aerated, and showed no evidence of consolidation. The bronchial arteries were markedly dilated and hypertrophied, and measured 4 to 5 mm. in diameter. Microscopic examination of the lungs showed no abnormality.

Kidneys.—The kidneys were tremendously hypertrophied, and, together, weighed 450 Gm. Grossly they were otherwise normal. Microscopic examination showed very severe passive venous engorgement and capillary congestion. Many of the glomeruli were normal except for congestion. Others, however, showed an increase in both endothelial cells and leucocytes which was suggestive of a grade I acute glomerular nephritis. Still others were partially or completely hyalinized. Many of the tufts showed only focal fibrosis or capsular thickening. There were no vascular changes. The changes are best interpreted as being consistent with marked passive congestion, healed embolic nephritis, and terminal acute glomerular nephritis.

Brain.—In the right temporal region of the brain there was an abscess 4 to 6 cm. in diameter, filled with a soft, gelatinous blood clot and foul-smelling gray pus. There was no overlying meningitis.

Bone Marrow.—The bone marrow was deep red in color, and showed marked hyperplasia, especially of the erythrocyte series, with replacement of the fat cells.

ANATOMIC DIAGNOSES

Congenital heart disease: Tetralogy of Fallot (hypertrophy of right ventricle, dextroposition of aorta, interauricular and interventricular septal defects, bicuspid pulmonary valve, with stenosis).

Rheumatic heart disease.

Chronic rheumatic endocarditis of the aortic, tricuspid, and (?) pulmonary valve. Endocarditis, healed bacterial, with calcification, of the pulmonary valve.

Nephritis (healed embolic and acute glomerular, grade I).

Cerebral abscess, right temporal lobe.

Chronic passive congestion, marked, of the liver, spleen, and kidneys.

Hypertrophic pulmonary osteoarthropathy, marked.

Hyperplasia of bone marrow.

Cyanosis.

METABOLIC STUDIES

METHODS

During the first admission the patient was transferred to the research ward, and controlled studies of intake and output were made during six periods. The customary precautions were exercised. The preparation of food, collection of excreta, and the methods for analysis of the various constituents have been described.^{6, 7} A preliminary period of three days was allowed for the patient to approach equilibrium on the constant diet. The diet contained 288 Gm. of carbohydrate, 38 Gm. of fat, and 61 Gm. of protein. The calculated calories amounted to 1,750. After ingestion of the diet for three days, Period 1 was begun Nov. 26, 1937. It continued for five days, was followed by a second five-day period, and then by a four-day period. Period 4 was begun Dec. 10, 1937. On that day 10 Gm. of urea were given by mouth. On the first and second day of Period 5, 8 Gm. of ammonium chloride were given orally. On the first and second day of Period 6, 20 Gm. of sodium bicarbonate were given by mouth. This period terminated after three days. All of the urine excreted was saved and partitioned into twenty-

four-hour specimens. An aliquot of each day's sample was analyzed for the various acid and base constituents. An aliquot of the diets and stools was analyzed for each period. The observations are summarized in Table I. Arterial and femoral venous blood was drawn on several occasions. Oxygen capacity, oxygen and carbon dioxide content of whole blood, and the concentration in the serum of total fixed base, sodium, potassium, calcium, chloride, bicarbonate, phosphate, and protein were ascertained (Table II). Experimental observations upon equilibrated whole blood were collected for the construction of oxygen and carbon dioxide dissociation curves.

RESULTS

The concentration of the constituents of the blood, especially oxygen and carbon dioxide, showed marked variations from normal. The oxygen capacity, 32.7 to 35.4 volumes per cent, as well as the oxygen saturation of arterial blood, 58 to 61 per cent, are critical values. Greater variations from the normal have not been reported, and most likely are incompatible with life.

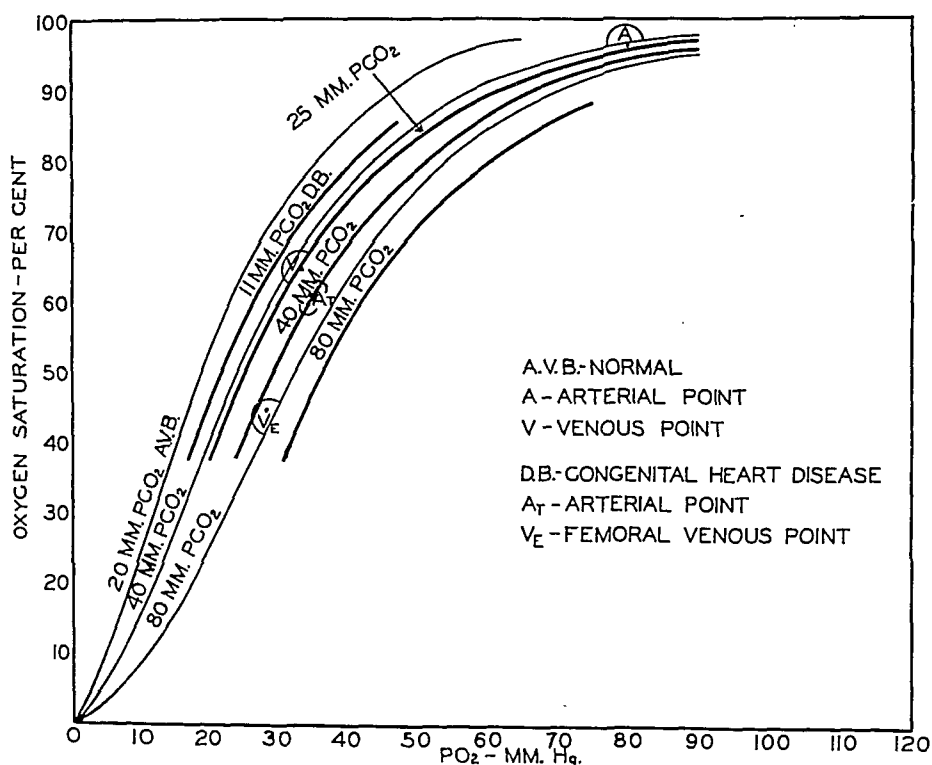


Fig. 3.—Oxygen dissociation curves of patient D. B. and normal control A. V. B.

Oxygen dissociation curves constructed at 11, 25, 40, and 80 mm. partial pressure of carbon dioxide, respectively, are given in Fig. 3. The 20, 40, and 80 mm. curves of a normal person are incorporated in the figure for comparison. The arterial (A) and venous (V) points for normals are plotted. The arterial point (A_t) for D. B. was obtained from data on samples of peripheral arterial blood. The oxygen saturation averaged approximately 62 per cent, except for the sample taken

TABLE I

PERIOD	DATE (1937)	CONSTITUENT	DIE-TARY IN-TAKE	EX-TRA-DIE-TARY IN-TAKE	URI-NARY OUT-PUT	FECAL OUT-PUT	DAILY BAL-ANCE	COMMENTS
1	November 26-December 1	Sodium (m.eq.)	288	171	389	31	+ 7.8	
		Potassium (m.eq.)	275		179	57	+ 7.8	
		Calcium (m.eq.)	32		1	47	- 3.2	
		Chloride (m.eq.)	287	171	449	11	- 0.5	
		Phosphate (mg.)	3,720		2,373	1,600	- 50.	
		Nitrogen (Gm.)	50.0		44.2	4.7	+ 0.2	
2	December 1-6	Sodium (m.eq.)	277	171	433	23	- 1.6	
		Potassium (m.eq.)	255		170	51	+ 6.8	
		Calcium (m.eq.)	33		2	46	- 3.0	
		Chloride (m.eq.)	312	171	461	9	+ 2.6	
		Phosphate (mg.)	3,205		2,439	1,288	-124.	
		Nitrogen (Gm.)	48.3		44.7	5.2	- 0.3	
3	December 6-10	Sodium (m.eq.)	217	137	322	16	+ 4.0	
		Potassium (m.eq.)	199		144	36	+ 4.8	
		Calcium (m.eq.)	27		2	34	- 2.2	
		Chloride (m.eq.)	235	137	363	3	+ 1.5	
		Phosphate (mg.)	2,664		1,688	1,123	- 34.	
		Nitrogen (Gm.)	41.4		36.0	3.8	+ 0.4	
4	December 10-14	Sodium (m.eq.)	228	137	292	11	+ 15.5	10 Gm. urea, orally
		Potassium (m.eq.)	219		152	29	+ 9.5	
		Calcium (m.eq.)	25		1	22	+ 0.5	
		Chloride (m.eq.)	243	137	363	4	+ 2.8	
		Phosphate (mg.)	2,706		1,447	730	+132.	
		Nitrogen (Gm.)	38.7	4.8	39.2	2.7	+ 0.4	

TABLE I—CONT'D

PE- RIOD	DATE (1937)	CONSTIT- UENT	DIE- TARY IN- TAKE	EX- TRA- DIE- TARY IN- TAKE	URI- NARY OUT- PUT	FECAL OUT- PUT	DAILY BAL- ANCE	COMMENTS
5	December 14-18	Sodium (m.eq.)	231	137	423	19	- 18.5	16 Gm. am- monium chloride, orally
		Potassium (m.eq.)	226		193	52	- 4.7	
		Calcium (m.eq.)	25		1	33	- 2.5	
		Chloride (m.eq.)	249	436	608	10	+ 16.8	
		Phosphate (mg.)	2,912		1,926	1,043	- 14.	
		Nitrogen (Gm.)	43.1	4.1	40.7	4.4	+ 0.5	
6	December 18-21	Sodium (m.eq.)	168	579	257	34	+152.0	40 Gm. so- dium bi- carbonate, orally
		Potassium (m.eq.)	164		77	40	+ 15.7	
		Calcium (m.eq.)	18		1	35	- 6.0	
		Chloride (m.eq.)	173	103	215	8	+ 15.6	
		Phosphate (mg.)	2,202		855	1,292	+ 15.	
		Nitrogen (Gm.)	30.8		29.5	5.0	- 1.2	

just before death. The venous (V_e) point was obtained from analysis of femoral venous blood.

The cell volume was the greatest that we have observed in any pathologic state. The cell volume was 85 per cent or more, except for a short time after the withdrawal of large amounts of blood for chemical studies. The erythrocytes were but slightly hypochromic,⁸ and contained almost a normal concentration of hemoglobin.

There was a profound acidosis. The carbon dioxide content of the serum was reduced about 8 m.M. per liter (18 volumes per cent) below the average normal. The pH_s was less than 7.30. The ingestion of 16 Gm. of ammonium chloride accentuated the acidosis, whereas the ingestion of 40 Gm. of sodium bicarbonate increased the carbon dioxide content of whole blood above normal and restored the pH_s to normal. The content of bases and the other acid constituents in the serum was ascertained, and, except for potassium and phosphate, there was no significant deviation from the normal. The concentration of potassium was as high as 7.4 m.eq. per liter, and of phosphate, 2.2 m.eq. per liter. Since the nonprotein nitrogen varied from 45 to 54 mg. per 100 c.c., it was assumed that the phosphate elevation, also, was associated with renal insufficiency.

TABLE II
OBSERVATIONS ON ARTERIAL AND VENOUS BLOOD OF D. B.

DATE	SOURCE	WHOLE BLOOD				TRUE PLASMA OR SERUM											PULMONARY VENOUS PH ₂ *	PERIPHERAL ARTERIAL PH ₂	COMMENTS	
		OXYGEN CAPACITY (VOL. PER CENT)	OXYGEN SATURATION (PER CENT)	CELL VOLUME (PER CENT)	TOTAL CARBON DIOXIDE (M.L. PER LITER)	TOTAL FIXED BASE (M.EQ. PER LITER)	SODIUM (M.EQ. PER LITER)	POTASSIUM (M.EQ. PER LITER)	CALCIUM (M.EQ. PER LITER)	TOTAL CARBON DIOXIDE (M.L. PER LITER)	CHLORIDE (M.EQ. PER LITER)	PHOSPHATE (M.EQ. PER LITER)	PROTEIN (GM. PER 100 G.C.)	NONPROTEIN NITROGEN (MG. PER 100 G.C.)	URATE (MG. PER 100 G.C.)	ARTERIAL PCO ₂ (M.M. HG.)				ALVEOLAR PCO ₂ (M.M. HG.)
Nov. 9, 1937	Brachial artery	35.4	61	86.8	13.9	156.8	135.0			16.7	106.5		5.6			38	25	7.25	7.45	After 40 hours of breathing a 50 per cent oxygen mixture
Nov. 19, 1937	Brachial artery	35.3	61	85.6	13.9	153.1	140.3			17.7	106.9		6.0			37		7.28	7.47	
Nov. 19, 1937	Femoral vein	34.2	48	84.6	15.9															
Nov. 22, 1937	Brachial artery	34.8	69		14.5															
Nov. 22, 1937	Femoral vein	34.6	44		17.5															
Dec. 10, 1937	Femoral artery	35.0				149.0	135.9	6.3	4.5	20.2	105.6	1.7	5.6	49	11.9					10 Gm. of urea taken orally on Dec. 10, 1937 16 Gm. of ammonium chloride taken orally during 48 hours pre- vious to withdrawal of blood
Dec. 14, 1937	Femoral artery	34.1		84.3		150.8	136.0	5.1		21.6	104.9	2.2	5.6	43	13.5					
Dec. 16, 1937	Femoral artery	33.5		81.8	11.2	148.9	132.7	7.4		13.8	113.7	1.6	6.0	49	11.1	36	18	7.19	7.51	
Dec. 20, 1937	Femoral artery	32.7		77.1	22.7	157.5	141.5	5.4	4.2	31.9	101.0	1.4	5.2	42	8.6	52	34	7.41	7.60	40 Gm. of sodium bi- carbonate taken orally during 48 hours pre- vious to withdrawal of blood
Feb. 2, 1938	Anti- cubital vein	34.6		85.5																
Nov. 19, 1938	Femoral artery	33.3	58	85.0						17.4			5.6	54						

*Calculated from alveolar pCO₂ and the carbon dioxide dissociation curves. It was assumed that the pulmonary venous blood was 95 per cent saturated with oxygen.

The urinary excretion of ammonia and titratable acid, and its pH, were remarkably constant. In the first four periods the daily ammonia production ranged from 23 to 29 m.eq. It was little affected by the ingestion of 8 Gm. of urea. After ammonium chloride ingestion, it increased to a maximum of 59 m.eq. Following the ingestion of sodium bicarbonate, it decreased to 9.8 m.eq. The titratable acid and hydrogen-ion concentration showed little variation except after sodium bicarbonate ingestion. There was a slight negative calcium balance in most periods (Table I). This has been the usual finding in our experience with patients on a constant metabolic regime, especially those whose activity is restricted. The patient was in nitrogen and phosphate balance throughout the study. A positive potassium balance was noted in all periods except Period 5. Presumably, this was associated with the elevated potassium in the serum. After the ingestion of urea and sodium bicarbonate there was a significant retention of sodium. A negative balance followed ammonium chloride ingestion. The patient was in positive chloride balance in Periods 5 and 6. Equilibrium was established in the other periods.

DISCUSSION

The history and physical signs made a diagnosis of congenital heart disease in our case quite certain. It was predicted that the anatomic defects would be similar to those characterized as the tetralogy of Fallot.⁹ This was confirmed at post-mortem examination, at which the following cardiac abnormalities were evident: hypertrophy of the right ventricle, dextroposition of the aorta, pulmonary stenosis, and an interventricular septal defect. There was, in addition, an interauricular septal defect. The age at which the patient died is above the average but does not approach the longevity reported elsewhere. Many patients with the tetralogy of Fallot die before adolescence, but some live to the third and fourth decade; the record to date is fifty-nine years and eight months,¹⁰ but one of us (P. D. W.) has under observation at present a woman, 66 years of age, with undoubted clinical evidence of the disease, who is still in fair health; evidently it is a mild case.

It is of interest to trace briefly the history of the recognition of the congenital cardiac anomaly now widely known as the tetralogy of Fallot. Fallot, in 1888, did not pretend that he was the first to describe the anomaly, but he did a service to medicine by pointing out that at least three-quarters of all persons who show cyanosis and clubbing of the fingers from infancy do have this tetralogy of defects. Thus, without further ado or study, the chances are at least 3 to 1 that such persons have the anomaly; physical examination (showing little evident cardiac enlargement and only a pulmonary systolic murmur), the electrocardiogram (with its high degree of right axis deviation and normal rhythm),

and the roentgenographic contour of the heart (more or less sabot-shaped, with prominent aorta and small pulmonary arterial tree) confirm the diagnosis.

As one consults early medical literature, one finds more and more case reports, autopsies, in the main, of what has since been called the tetralogy of Fallot. We have found no reference to this syndrome, however, before the eighteenth century. Bonetus¹¹ did not describe such a case in his *Sepulchretum*, in 1679, nor did Mangetus¹² in the second edition of the *Sepulchretum*, in 1700. In the eighteenth century there was the report by Morgagni¹³ of a case of pulmonary stenosis in a girl, aged 16 years, who had been cyanotic since birth. The right ventricle and right auricle were very large, and there was said to be a patent foramen ovale. Sandifort,¹⁴ in 1777, reported similar abnormalities in a boy who died at the age of 12 years. Early in the nineteenth century the physiologic disturbances associated with congenital heart disease were presented ably by Farre.¹⁵ He reported several cases of cyanosis and clubbed fingers in which the tetralogy was demonstrated at post-mortem examination. Gintrac,¹⁶ in 1824, and Peacock,¹⁷ in 1858, described additional cases. It was not until 1888 that Fallot's⁹ description was published, and this dates the eponym.

Our patient was a semi-invalid during the last year of his life. He refused, however, to be considered as one. He was above the average scholastically and, in spite of the physical handicap, made a commendable record at his studies. On physical examination, the clubbing of the fingers was striking. It was largely soft tissue hypertrophy, however, as no tufting of the terminal phalanges was evident roentgenologically. The external ears were paper-thin and prominent. The pigmentation of the skin of the extremities, which has been observed in other patients with morbus caeruleus,^{18, 19} as well as in patients suffering from chronic mountain sickness,⁵ presumably is associated with anoxemia and peripheral venous stasis.

It was believed, from the clinical evidence, that the patient had experienced attacks of acute rheumatic fever between the ages of 10 and 12, as well as subacute bacterial endocarditis while under observation eight or nine months before death. The presumptive diagnosis of subacute bacterial endocarditis was based upon the presence of fever, hematuria, failing cardiac reserve, pleural pain, with a friction rub, and abdominal cramps (? embolic). If bacterial endocarditis develops in a case of congenital heart disease, usually it is a terminal,²⁰ rather than an intercurrent, event. Our patient was not treated with any specific drug, such as a sulfonamide derivative, or with any immune vaccine or serum. Nevertheless, the calcified vegetations discovered at the post-mortem examination strongly supported the clinical observation that he had recovered from an endocarditis. It has been stated previously that several blood cultures showed no growth. The failure to cultivate from

the blood and identify a pathogenic organism is evidence against, but does not rule out, the diagnosis of subacute bacterial endocarditis, especially in congenital heart disease. In fact, it may be extremely difficult to isolate the organism in subacute bacterial endocarditis which is superimposed upon a congenitally deformed heart.²¹ Since rheumatic lesions, as well as those of subacute bacterial endocarditis, may calcify, the question of which malady was responsible must be answered by the pathologic studies. These offer conclusive evidence that the patient suffered first from rheumatic heart disease and later from subacute bacterial endocarditis and that the bacterial endocarditis increased the stenosis of the already congenitally stenosed pulmonary valve.

One observation of obscure significance during life was the constant, well-marked, early diastolic murmur at the base of the heart, which was interpreted as due to aortic regurgitation, despite a normal pulse pressure. We did not know whether this aortic regurgitation was to be ascribed to a complicating rheumatic aortic valve disease, or to dilatation of the aortic ring simply as the result of the markedly increased aortic output. It turned out that the latter was the correct explanation; we have encountered it in one other case of the tetralogy of Fallot.

Death was precipitated by a cerebral abscess. Although the cardiac reserve was strained to the breaking point, death was not caused by cardiac failure, *per se*. Just as the blood appeared to be sterile during what we deem was an attack of endocarditis, so was it sterile when a diagnosis of cerebral abscess was apparent, and, at autopsy, no growth was seen in a culture of the blood from the chambers of the heart. A culture from the cerebral abscess alone showed pathogenic organisms. These were colon bacilli and Gram-positive cocci in clusters. The incidence of cerebral abscess in patients with a sizable septal defect is believed by Abbott to be more than coincidence.²² Rabinowitz and his associates²³ were willing to go so far as to state that "the presence of an idiopathic brain abscess should lead one to suspect the possibility of the presence of a congenital cardiac defect."

The concentration of the gases in the blood and the results of the metabolic studies were as interesting as the clinical and pathologic observations. It is believed by us that the concentration of the gaseous constituents of the arterial blood approached the extreme limit of variation from the normal, beyond which life cannot be maintained. In spite of the deviations from normal, the body had made a remarkably adequate adjustment, and death was caused by an infection in the brain, not directly from inadequate oxygen transport or recurring cardiac failure.

The cell volume varied from 82 to 87 per cent, and the oxygen capacity, from 32.7 to 35.4 vol. per cent. The concentration of hemoglobin in the whole blood increased the density to such an extent that the blood

seemed almost to congeal in the veins. The blood was so viscous that, during an arterial or venous puncture, the plunger of an oiled syringe had to be withdrawn forcefully in order to introduce blood into the barrel. The viscosity of the blood offered considerable peripheral resistance and imposed a real burden upon the myocardium.

The oxygen saturation of the arterial blood varied between 62 and 58 per cent. The former value was obtained when the patient was ambulatory; the latter was obtained only a few hours before death. Approximately a year elapsed between the two observations. Very few studies of the oxygen saturation of the arterial blood of patients with congenital heart disease have been reported since Van Slyke's development of the manometric blood gas analyzers made them possible. To the twenty cases reported in the literature we have added five of our own, and summarized the pertinent data in Table III. Certain data, only, on patients M. G., E. R., H. W., and D. S., who were seen by us, are included in the table. Other observations made upon these patients will be described in detail elsewhere.

It is apparent that, when the arterial oxygen saturation approaches 60 per cent, oxygen transport, even at rest, becomes a critical problem, and life cannot long be maintained. A similar conclusion was reached in our studies in the Chilean Andes. The lowest saturation in a permanent resident at 17,500 feet was 67 per cent.⁵ At 20,100 feet the oxygen saturation of the arterial blood of a temporary resident was 55 per cent.²⁴ Both observations were made on persons who were healthy and physically sound. The permanent residents at 17,500 feet admitted no symptoms except dyspnea on exertion. The temporary resident had no distressing symptoms while living at 17,500 feet, but complained bitterly of headache, anorexia, and fatigue after living at 20,100 feet for twenty-four hours with an oxygen saturation of 55 per cent. The subject remained ambulatory in spite of these symptoms and an uncomfortably low environmental temperature. It is noteworthy that patients with morbus caeruleus may remain ambulatory with an improperly functioning heart and a blood oxygen saturation which corresponds to that at an altitude of approximately 4 miles. Of course, many patients with congenital heart disease become adjusted to a progressive diminution in the partial pressure of oxygen in the blood over a long period of time, just as residents at high altitudes become adjusted.

These studies cast considerable doubt upon the assumption that the symptoms which are sometimes attributed to chronic carbon monoxide poisoning²⁵ are produced by recurrent anoxemia, per se. It cannot be denied that repeated exposure to small amounts of carbon monoxide may produce a syndrome that is recognized as carbon monoxide poisoning. The symptoms, however, should be attributed to some factor or factors in addition to mild anoxemia. The observations of Asmussen and Chiodi,

TABLE III
OBSERVATIONS ON BLOOD GAS CONCENTRATIONS IN PATIENTS WITH CONGENITAL HEART DISEASE, AS REPORTED IN THE LITERATURE

AUTHORS	CASE	AGE (YEARS)	SEX	PULMO- NARY VEN- TILATION (LITERS PER MINUTE)	ARTERIAL BLOOD			ARTERIAL pH _s	ALVEOLAR pCO ₂ (MM. HG.)	COMMENTS
					OXYGEN CAPACITY (VOLUMES PER CENT)	OXYGEN SATURA- TION (PER CENT)	CARBON DIOXIDE CONTENT (VOLUMES PER CENT)			
Normal mean					21.0	95	48	7.40	40	
Campbell, et al. ⁴²	No. 15	20	♂	9	24.7	69	36.9	7.31	24	Patent septum, pulmonary ste- nosis
	No. 17	35	♂	6	27.9	77	39.6	7.32	25	Patent septum, pulmonary ste- nosis
	No. 43	24	♂		31.5	84	35	7.30		Patent septum, pulmonary ste- nosis
Raab, et al. ¹⁰		15	♂		31.6	75				Tetralogy of Fallot
Henderson ¹					34.0	76	38.5	7.27	36	Tetralogy of Fallot
Mainzer ³⁵		25			25.3	66	37.0	7.44		Roger's disease
D'Autrebände, et al. ⁴³	No. 1	12	♂	5	32.3	63*	28*	7.37	23	Patent septum, pulmonary ste- nosis
	No. 2	13	♀	5	27.2	70*	33.6*	7.40	25	Cyanosis only on exertion
	No. 3	19	♂	13	29.8	81*	34.3*	7.37	27	
		26	♂	15	35.2	62	27.5	7.17	26	Patent septum, transposition of great vessels
Hitzenberger and Tuckfeld ³⁹		12	♀	9	33.8	60	38.6		23	Tetralogy of Fallot
Richards, et al. ²⁸	A. S.	23	♀		26.3	64				Tetralogy of Fallot
Segall ⁴¹	I. M.	22	♂	17	35.0	82	35.0	7.47	29	Patent septum, pulmonary ste- nosis
Meyer ³⁴										
Uhlenbruck ⁴⁴	M. S.	3	♀		31.9	88	35	7.38	23	Tetralogy of Fallot
Schoen and Derra ⁴⁵	No. 1	23	♂		18.4	82	42.0			Patent septum
	No. 2	15	♀		19.9	75	41.4		29	Patent septum
	No. 3	21	♂		29.8	72	47.3			Patent septum
	No. 4	21	♂	6	30.8	56	32.7		28	Pulmonary stenosis
Mayer and Israel ⁴⁶	M. L.	24	♀		17.9	69	46.7			Tetralogy of Fallot
Pijoan and Berard ⁴⁷		23	♀		23.0	78				Tetralogy of Fallot
Talbott, et al.	D. B.	19	♂		35.4	61	31.1	7.25	25	Tetralogy of Fallot
	M. G.	35	♀		32.2	60	32.9	7.30		No anatomic diagnosis made. Morbus caeruleus
	E. R.	27	♂		31.5	84	36.6			No anatomic diagnosis made. Morbus caeruleus
	H. W.	21	♀		28.1	79	38.2	7.34		Probably tetralogy of Fallot
	D. S.	38	♂		24.1	84	38.6	7.38		No anatomic diagnosis made. Morbus caeruleus

*Observations reported by authors to be unreliable.

recently reported,²⁶ support this contention. These investigators studied oxygen deficiency in normal human subjects by two different procedures: (1) by replacing a part of the oxyhemoglobin with carbon monoxide hemoglobin, and (2) by allowing the subject to breathe a gas mixture which was low in oxygen. Anoxemia produced by partial carbon monoxide poisoning elicited little or no respiratory response and had little or no effect upon cardiac output. On the other hand, a diminished partial pressure of oxygen in the inspired air produced pronounced hyperventilation and an increase in cardiac output.

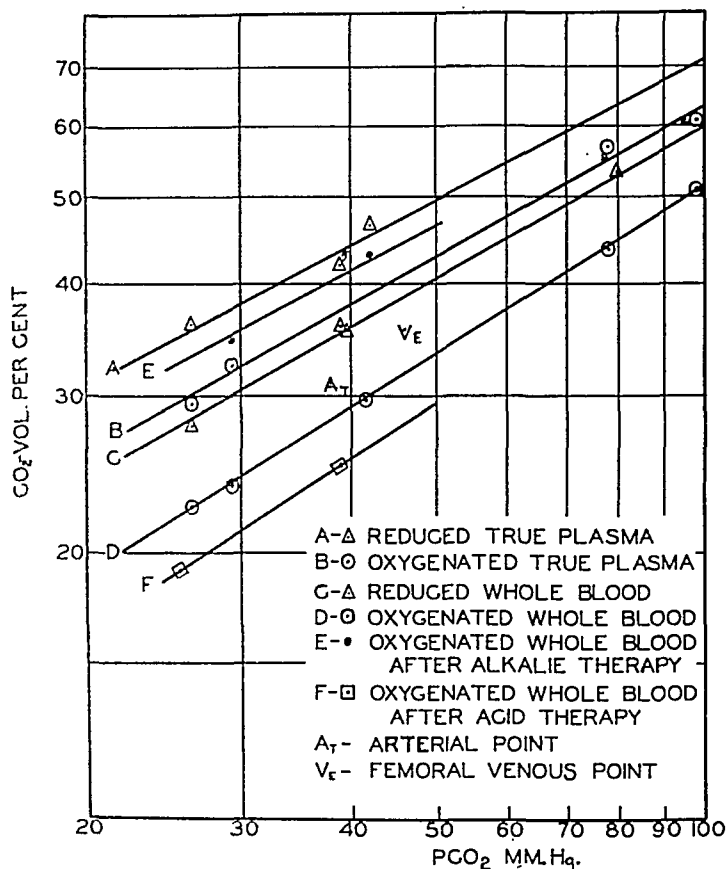


Fig. 4.—Carbon dioxide dissociation curves of patient D. B. plotted on logarithm paper.

Our patient with congenital heart disease was placed in an oxygen tent and allowed to breathe for forty hours a gas mixture which contained 50 per cent oxygen. No marked increase in the oxygen saturation of the arterial blood followed this treatment, and only slight symptomatic improvement was admitted. Hemsath, et al.,²⁷ and Richards, et al.,²⁸ have reported similar results. It is concluded that oxygen therapy is ineffective in increasing the transport of oxygen to the tissues of patients with a right-to-left heart shunt. The explanation is readily apparent. Oxygen therapy increased the partial pressure of oxygen only in the pulmonary circuit. In morbus caeruleus the arterial blood is saturated about as completely in these vessels as it is normally, even

though the saturation in the peripheral arteries is reduced considerably. Since oxygen therapy does not alter the arteriovenous shunt, it cannot be expected to increase the supply of oxygen to the tissues.

Femoral venous blood was investigated on two occasions. At the first observation the saturation of oxygen was 48 per cent, or approximately 20 per cent below normal. It decreased to 44 per cent following prolonged oxygen inhalation. This change is not significant.

There is some theoretical basis for the assumption that there may be a direct correlation between unsaturation of blood and increase in oxygen capacity in healthy persons. The Andean studies²⁴ showed that this assumption was a good approximation. The data on congenital heart disease are more discordant. The association of a serious disease with anoxemia is probably responsible for the wide scattering.

It would be interesting and might be clinically important if information were available concerning the amount of blood that passes through the cardiac shunt. An earnest, but unsuccessful, attempt was made to measure the cardiac output with the acetylene method. We were forced to rely, therefore, upon the formula described by Lundsgaard and Van Slyke,²⁹ which is approximate and not precise. The application of our data to the formula indicated that nearly three-fourths of the blood which circulated through the heart was not aerated in the lungs.

Changes in the carbon dioxide content of the arterial blood are as characteristic of morbus caeruleus as are changes in oxygen content. When the malady is advanced and the diagnosis is obvious clinically, there are a diminished content of carbon dioxide in the blood, a diminution in the height of the carbon dioxide dissociation curve (Fig. 4), and a decrease in the partial pressure of alveolar carbon dioxide.³⁰⁻³² Abbott,²² with the collaboration of Boothby, was the first to consider theoretically the variation in carbon dioxide during the respiratory cycle in congenital heart disease. In 1912 they postulated an increase above normal in the difference in carbon dioxide content of arterial and venous blood. The difference is approximately 4 volumes per cent³³ in healthy persons, whereas, in the case of D. B., it was nearly 9 volumes per cent. The total carbon dioxide content of the arterial blood was markedly reduced. The average range for normal persons is from 46 to 54 per cent. We have chosen 48 as a mean value. One of the lowest values for any patient with congenital heart disease listed in Table III was observed in the case of D. B. This was 31.1 volumes per cent. Few exceeded 40 volumes per cent. The partial pressure of carbon dioxide in the alveolar air showed a similar decrease. The average value for normals is approximately 40 mm. Hg. It is usually below 30 mm. in patients with advanced morbus caeruleus.

Finally, variations in the hydrogen-ion concentration may be calculated from the carbon dioxide data. It is the custom when studying trained

subjects without a cardiac or a pulmonary defect to make the calculation for pH_s from the observations on alveolar pCO_2 and the carbon dioxide content of arterial blood.³³ An alternate procedure is to construct a set of carbon dioxide dissociation curves, ascertain the carbon dioxide content of arterial blood, and locate the arterial point on the constructed graph. The calculated pH_s should be the same by either method. If the pH_s of arterial blood is desired in cases of morbus caeruleus, the second procedure must be employed. The alveolar pCO_2 cannot be utilized because it does not represent the partial pressure of carbon dioxide in the peripheral arterial blood, but only that of arterialized blood in the pulmonary circuit. All of the pH_s values given in Table III, except that of Meyer,³⁴ were obtained by this procedure. Except for this observation and that of Mainzer,³⁵ all of the values for pH_s are 7.40 or less. The lowest was 7.25, in our case (D. B.).

It is apparent that the blood gas concentrations in patients with morbus caeruleus deviate consistently from the normal, and this, we believe, is characteristic. They include an increased oxygen capacity, a decreased oxygen saturation and a decreased carbon dioxide content of arterial blood, a decreased partial pressure of alveolar pCO_2 , and a decreased arterial pH_s .

The pathogenesis of the unsaturation of arterial blood is most likely mechanical. Unsaturated venous blood from the right side of the heart is shunted through the septal defect or into the aorta, and thence into the peripheral circulation without passing through the lungs. The physiologic and pathologic effects cannot be altered as long as the anatomic defects persist. A progressive increase in the oxygen capacity follows the prolonged anoxemia. The mechanism of the increase is probably similar to that observed in dwellers at high altitudes. The pathogenesis of the variation from normal in carbon dioxide content and pH_s is more difficult to ascertain.

The lowering of the carbon dioxide content of the blood and the decreased partial pressure of alveolar carbon dioxide have been attributed to hyperventilation. Such a phenomenon may contribute, but it is not solely responsible. Uncomplicated hyperventilation does not produce acidosis, as is observed in congenital heart disease, but alkalosis.³⁶ Furthermore, only a portion of the blood which enters the peripheral arterial system traverses the pulmonary circuit and is available for exposure to hyperventilation. Nor is anoxemia mainly responsible for the changes in carbon dioxide. The profound anoxemia at high altitudes²⁴ is associated with parallel decreases in alveolar pCO_2 and the carbon dioxide content of arterial blood. The ratio of free to combined carbon dioxide tends to remain constant, so that the pH_s shows little variation from normal. Thus, neither hyperventilation nor anoxemia is responsible for an uncompensated acidosis.

An increased concentration of acid in the blood could account for all of the variations. No adequate study of the acid-base balance of the blood of patients with congenital heart disease has ever been reported. Our observations (Table II) are comprehensive and instructive. The concentrations of the individual bases show a slight decrease in serum sodium and a slight increase in serum potassium. The sum of the bases, however, although it is at the lower border of normal, is not below normal. A deficiency of base, therefore, cannot be held responsible for the acidosis and diminished alkaline reserve. The acid side of the balance column should be reviewed next. Complete acid-base data for Dec. 10, 1937, are assembled in Table IV. The concentrations of all of the constituents are expressed in milliequivalents per liter. In this sample of serum the concentrations of chloride and phosphate were normal, whereas that of proteinate was a low normal. The concentration of bicarbonate was reduced about 10 m.M. per liter; this amount had been replaced by an equivalent amount of undetermined acid. This sample of blood does not represent the extreme, for other samples from D. B. showed even greater amounts of undetermined acids. The nature of the undetermined acid is not known. Ketone bodies were not present in any routine urine specimen that was examined. The content of lactic acid was not ascertained, but it is unlikely that this acid accounted in large part for the undetermined excess. Increased production of organic acids, as well as diminished renal excretion of these and normally appearing acids, was probably operative. The evidence in favor of an increased production of organic acids is indirect. In other conditions associated with renal failure, such as bichloride of mercury poisoning,³⁷ an increased production of organic acid has been assumed.

TABLE IV
ACID-BASE CONSTITUENTS OF THE SERUM ON DEC. 10, 1937
(Concentrations are expressed in milliequivalents per liter.)

BASES		ACIDS	
Sodium	135.9	Chloride	105.6
Potassium	6.3	Bicarbonate	18.2
Calcium	4.5	Proteinate	12.8
Magnesium	1.5*	Phosphate	1.7
Total fixed base	148.2		138.3

*Assumed.

Study of renal function and quantitative estimation of renal insufficiency in patients with congenital heart disease has not been pursued intensively by many investigators. Mainzer,³⁵ Irvine-Jones,³⁸ Hitzenger and Tuckfeld,³⁹ Leadingham,⁴⁰ and Segall⁴¹ are the only authors that we have discovered who have referred to the subject. In a survey of 100 cases of congenital heart disease, Irvine-Jones noted that albuminuria had been reported in thirteen. Few showed cylinduria. It

was apparent to him that the presence of albuminuria was associated with a rapidly fatal outcome. Albuminuria, erythrocytes, and casts were noted in the urine of the patient reported by Segall. At autopsy the kidneys showed parenchymatous degeneration, but no evidence of nephritis. Similar clinical observations were made in Mainzer's case, but no autopsy findings were reported. Hitzenger and Tuckfeld³⁹ noted large amounts of albumin and many erythrocytes and leucocytes in the urine of the patient described by them. The blood pressure was 140/115. Since the patient was only 26 years of age, the elevation of the diastolic pressure, together with the urinary abnormalities, points toward severe renal damage. The concentrations of the gas constituents in the blood were similar to those in our case.

Evidence of renal insufficiency in our patient was striking and persistent. The concentration of nonprotein nitrogen in the serum varied between 42 and 54 mg. per 100 c.c. during the year before death. The maximum specific gravity during two urine concentration tests was only 1.018. The ability to excrete phenolsulphonphthalein was impaired likewise. In the first twenty-five minutes after the intravenous injection of the dye, only 20 per cent was excreted, or 0.8 per cent per minute. A normal person should excrete 1.7 c.c. per minute during the first fifteen-minute period. Finally, intravenous pyelography showed poor excretion of diodrast.

The intake and output studies furnished additional evidence that the kidneys functioned poorly and were unable to participate effectively in regulating the acid-base balance of the blood. The pH and titratable acid of the urine were fixed except during the period of sodium bicarbonate ingestion. It is significant that the ingestion of ammonium chloride had little effect upon the urinary pH. It is believed that the above-mentioned values were constant because of a decrease in ability to form ammonia. Ammonia excretion was increased above the fixed daily amount only after the ingestion of ammonium chloride. Even these variations were not great. It is possible that the kidneys had become intolerant to the persistent acidosis and were less labile in the formation of ammonia than formerly. A complicating and equally important factor in the pathogenesis of the renal insufficiency was anoxemia. It is presumed by us that anoxemia may produce disturbances in kidney function without underlying, demonstrable, morphologic changes. At least it can be stated that at autopsy no anatomic changes were observed in the kidneys which could explain all of the above-mentioned findings.

It is regrettable that the clearance rates of inulin and creatinine were not ascertained in the case of D. B. These observations were collected on E. R., however, and the results are probably applicable. E. R. had morbus caeruleus, but was less handicapped than D. B. The clinical evidence of renal insufficiency was similar. The inulin clearance of the

plasma in the case of E. R. was 65 c.c. per minute, and, of creatinine, 83 c.c. per minute. The normal values are 100 c.c. and 140 c.c., respectively. It is to be hoped that further observations on renal function in cases of morbus caeruleus will be made in the future.

SUMMARY

Clinical, metabolic, and pathologic studies of a patient with advanced morbus caeruleus (tetralogy of Fallot) are reported. The patient died at the age of 19, and had been cyanosed since the age of 2. He was proficient scholastically, and, until a year before death, suffered a minimum of handicap from his malady. He was thought to have had rheumatic fever at the age of 9 and subacute bacterial endocarditis during his last year of life. A colon bacillus abscess of the cerebrum was immediately responsible for death.

The metabolic investigations revealed a profound variation from the normal in the acid-base equilibrium of the body, and changes in renal function. As much as 75 per cent of the blood in the cardiac chambers was thought to traverse a right-to-left shunt. The oxygen saturation of the arterial blood varied between 62 and 58 per cent. These are critical levels for human existence. The oxygen capacity was about 35 volumes per cent. The carbon dioxide content of the arterial blood was less than 33 volumes per cent. The arterial pH_s was less than 7.29. A profound, uncompensated acidosis was attributed to the increased concentration of undetermined acids and failure of the respiratory center to maintain the usual balance between free and combined carbon dioxide. The functional insufficiency of the kidneys was attributed to anoxemia, venous congestion, and acidosis.

REFERENCES

1. Henderson, L. J.: Sur l'application de la méthode nomographique à l'étude des phénomènes respiratoires dans le sang, *Compt. rend. Acad. d. sc.* 180: 2066, 1925.
2. Bock, A. V., Dill, D. B., Edwards, H. T., Henderson, L. J., and Talbott, J. H.: On the Partial Pressures of Oxygen and Carbon Dioxide in Arterial Blood and Alveolar Air, *J. Physiol.* 68: 277, 1929.
3. Dill, D. B., Edwards, H. T., Folling, A., Oberg, S. A., Pappenheimer, A. M., Jr., and Talbott, J. H.: Adaptations of the Organism to Changes in Oxygen Pressure, *J. Physiol.* 71: 47, 1931.
4. Talbott, J. H.: Studies at High Altitudes. II. Morphology and Oxygen Combining Capacity of the Blood, *Folia haemat.* 55: 23, 1936.
5. Talbott, J. H., and Dill, D. B.: Clinical Observations at High Altitude. Observations on Six Healthy Persons Living at 17,500 Feet and a Report of One Case of Chronic Mountain Sickness, *Am. J. M. Sc.* 192: 626, 1936.
6. Talbott, J. H., Jacobson, B. M., and Oberg, S. A.: The Electrolyte Balance in Acute Gout, *J. Clin. Investigation* 14: 411, 1935.
7. Talbott, J. H.: Interpretation of Clinical Chemical Procedures, *Ohio State M. J.* 35: 137, 1939.
8. Weber, F. P.: Polycythaemia Anaemia Secondary to Congenital Cardiac Septal Defect, in Association With an Anaemia-Producing Agent, *Proc. Roy. Soc. Med.* 25: 789, 1932.
9. Fallot, A.: Contribution à l'anatomie pathologique de la maladie bleue (cyanose cardiaque), *Marseille méd.* 25: 77, 138, 207, 270, 341, 403, 1888.

10. White, P. D., and Sprague, H. B.: The Tetralogy of Fallot. Report of a Case in a Noted Musician Who Lived to His Sixtieth Year, J. A. M. A. 92: 787, 1929.
11. Bonetus, T.: Sepulchretum sive Anatomia Practica, ex Cadaveribus Morbo denatis, Geneva, 1679.
12. Mangetus, J. J.: Theopili Boneti, Sepulchretum, ed. 2, Geneva, 1700.
13. Morgagni, G. B.: De Sedibus, et Causis Morborum per anatomen indigatis, libri quinque, Venice, 1761.
14. Sandifort, E.: De rarissimo cordis vitio, Obs. Anat. Pathol., Luguni Batavorum, 1777.
15. Farre, J. R.: Pathological Researches. Essay I. On Malformations of the Human Heart, Illustrated by Numerous Cases, London, 1814.
16. Gintrac, E.: Observations et recherches sur la cyanose, ou maladie bleue, Paris, 1824.
17. Peacock, T. B.: Cases of Malformation of the Heart, London, 1864.
18. Volini, I. F., and Flaxman, N.: Tetralogy of Fallot. Report of a Case in a Man Who Lived to His Forty-First Year, J. A. M. A. 111: 2000, 1938.
19. Raab, W., Weiss, R., Löwbeer, B., and Rihl, J.: Untersuchungen über einen Fall von kongenitalem Herzvitium, Wien. Arch. f. inn. Med. 7: 367, 1923.
20. Harrison, W. F.: Congenital Heart Disease, Extreme Congenital Pulmonary Stenosis (Tetralogy of Fallot); Collateral Pulmonary Circulation; Massive Right-Sided Vegetative Endocarditis, AM. HEART J. 5: 213, 1929.
21. White, P. D., Boyes, J. H.: Subacute Bacterial (*Streptococcus Viridans*) Endocarditis and Endarteritis Involving the Tricuspid Valve and the Pulmonary Artery in a Unique Case of the Tetralogy of Fallot Complicated by Congenital Pulmonary Regurgitation, AM. HEART J. 7: 802, 1932.
22. Abbott, M.: Congenital Heart Disease, Nelson's Loose Leaf Medicine, 4: 207, 1932.
23. Rabinowitz, M. A., Weinstein, J., and Marcus, I. J.: Brain Abscess (Paradoxical) in Congenital Heart Disease, AM. HEART J. 7: 790, 1932.
24. Dill, D. B., Christensen, E. H., and Edwards, H. T.: Gas Equilibria in the Lungs at High Altitudes, Am. J. Physiol. 115: 530, 1936.
25. Beck, H. G.: The Clinical Manifestations of Chronic Carbon Monoxide Poisoning, Ann. Clin. Med. 5: 1088, 1927.
26. Asmussen, E., and Chiodi, H.: The Effect of Hypoxemia on Ventilation and Circulation in Man, Am. J. Physiol. 132: 426, 1941.
27. Hemsath, F. H., Greenberg, M., and Shain, J. H.: Congenital Cardiac Anomalies in Infants. Report of Five Cases—(1) Accessory Ventricle, (2) Tetralogy of Fallot With Right Aortic Arch and Redundant Left Ductus Arteriosus, (3) Tetralogy of Fallot With Anomalous Band in Right Auricle, (4) Complete Transposition of Arterial Trunks, and (5) Double Defect of Ventricular Septum, Am. J. Dis. Child. 51: 1356, 1936.
28. Richards, D. W., Jr., Riley, C. B., and Hiscock, M.: Congenital Heart Disease. Measurements of the Circulation, Arch. Int. Med. 47: 484, 1931.
29. Lundsgaard, C., and Van Slyke, D. D.: Cyanosis, Medicine 2: 1, 1923.
30. FitzGerald, M. P.: The Alveolar Carbonic Acid Pressure in Diseases of the Blood and in Diseases of the Respiratory and Circulatory Systems, J. Path. & Bact. 14: 328, 1910.
31. Straub, H., and Meier, K.: Blutgasanalysen, Deutsches Arch. f. klin. Med. 129: 54, 1919.
32. Govaerts, P., and Lequime, J.: La teneur du sang du coeur droit en acide carbonique dans la communication interventriculaire pure, Nederl. tijdschr. v. geneesk. 81: 260, 1937.
33. Henderson, L. J.: Blood. A Study in General Physiology, New Haven, 1928, Yale Univ. Press.
34. Meyer, P.: Hämodynamik und Hämophysikochemie bei einem Fall von Ventrikel-septumdefekt mit Pulmonalstenose, Ztschr. f. klin. Med. 120: 341, 1932.
35. Mainzer, F.: Analyse eines kongenitalen Herzfehlers (Zugleich ein Beitrag zur Bedeutung der Hämoglobinvermehrung bei Sauerstoffmangel), Ztschr. f. klin. Med. 108: 489, 1928.
36. Talbott, J. H., Cobb, S., Coombs, F. S., Cohen, M. S., and Consolazio, W. V.: Acid-Base Balance of the Blood in a Patient With Hysterical Hyperventilation, Arch. Neurol. & Psychiat. 39: 973, 1938.
37. Talbott, J. H., Coombs, F. S., and Consolazio, W. V.: Electrolyte Balance During Recovery From Mercury Bichloride Poisoning, Arch. Int. Med. 60: 301, 1937.

38. Irvine-Jones, E. I. M.: A Clinical Study of Congenital Heart Disease in Childhood, *AM. HEART J.* 2: 121, 1926.
39. Hitzengerber, K., and Tuckfeld, F.: Physikalisch-Chemische Verhältnisse des Blutes bei symptomatischer Polyglobulie, *Ztschr. f. klin. Med.* 113: 576, 1930.
40. Leadingham, R. S.: Tetralogy of Fallot: Report of a Case With Bacterial Endocarditis of the Pulmonary Valve and Collapse of Both Lungs, *Ann. Int. Med.* 4: 620, 1930.
41. Segall, H. N.: A Case of Tetralogy of Fallot: Clinicopathological Observations. Quantitative Studies of Circulation Rate and the Right to Left Shunt, *AM. HEART J.* 8: 628, 1933.
42. Campbell, J. M. H., Hunt, G. H., and Poulton, E. P.: An Examination of the Blood Gases and Respiration in Disease, With Reference to the Cause of Breathlessness and Cyanosis, *J. Path. & Bact.* 26: 234, 1923.
43. D'Autrebande, L., Marshall, W. R., and Meakins, J. C.: Studies of Circulation in Three Cases of Morbus Caeruleus, *J. Clin. Investigation* 8: 123, 1929.
44. Uhlenbruck, P.: Untersuchungen an einem autoptisch kontrollierten Fall von Pulmonalstenose, *Ztschr. f. Kreislaufforsch.* 19: 601, 1927.
45. Schoen, R., and Derra, E.: Untersuchungen über die Bedeutung der Zyanose als klinisches Symptom, *Deut. Arch. f. klin. Med.* 168: 52, 1930.
46. Mayer, C. P., and Israel, J. E.: La cianosis de una cardiopatía congénita. Estudio de los gases alveolares y de la sangre, *Rev. Asoc. méd. argent.* 48: 113, 1934.
47. Pijoan, M., and Bérard: Une nouvelle méthode de diagnostic des communications cardiaques arterio-veineuses, dans les cardiopathies congénitales, *Compt. rend. Soc. de biol.* 122: 411, 1936.

THE DISTRIBUTION OF SURFACE POTENTIAL ON THE CHEST IN INTRAVENTRICULAR BLOCK

A. BOHNING, M.D., L. N. KATZ, M.D., AND R. LANGENDORF, M.D.
CHICAGO, ILL.

RECENTLY we re-examined a series of 176 cases of intraventricular block,¹ and found that they fall into four major categories: the common, the uncommon, and the first and second indeterminate types.

In the *common type*, QRS₁ is upright and of the \wedge or $|/|$ type (with the first inverted phase tiny), and T₁ is inverted or diphasic, whereas QRS₃ is usually inverted and of the V or N type (but may be upright), and T₃ is usually upright (but may be inverted).

In the *first indeterminate type*, QRS₁ is upright and of the N or W type, and T₁ is inverted or diphasic; it differs from the common type in having a small inverted final phase; QRS₃ is usually inverted and of the N or M type, and T₃ is upright.

In the *second indeterminate type*, QRS₁ is diphasic and of the N type, with a deep, prolonged S₁; T₁ is usually upright. It differs from the uncommon type in having QRS₁ diphasic instead of mainly inverted.

In the *uncommon type*, QRS₁ is inverted or mainly inverted and of the N, or rarely V, type; usually there is a deep S₁, and T₁ is upright. QRS₃ is upright, and T₃ is usually inverted.

Measurements of the Q-E interval, namely, the interval from the onset of QRS to the onset of the subclavian arterial pulse, led to the conclusion that the common type of intraventricular block is most often associated with delay in the left ventricle, and that the uncommon and the two indeterminate types are not associated with delay in the left ventricle, hence, presumably, with delay in the right ventricle.¹ However, exceptions were found; especially frequent was the lack of evidence of Q-E prolongation in the common type of intraventricular block.

It seemed to us that this view could be checked further by ascertaining the distribution of the surface potential over the chest during various phases of the inscription of QRS, utilizing the method previously described by us.² For this purpose leads were taken entirely encircling the chest at the levels of the second and of the fourth intercostal spaces at the sternal margin in twelve of these cases of intraventricular block.

From the Cardiovascular Department, Michael Reese Hospital, Chicago.
Aided by the A. D. Nast Fund for Cardiac Research and the A. E. Kuppenheimer Fund.

Received for publication April 1, 1941.

RESULTS

Chest Lead Variations in the Different Types of Intraventricular Block.—Typical examples of the records obtained are shown in Figs. 1 to 6.* The chest leads in all of the types of intraventricular block which were studied showed a relationship to the limb leads similar to that reported for normal and hypertrophied hearts,² namely:

1. The left midaxillary chest lead at the level of the fourth intercostal space was usually almost the exact inverse of Lead I.

2. Leads at the right scapular region and the right posterior axillary area at the level of the second intercostal space were almost identical with Lead II.

3. Leads in equivalent positions on the left side were almost identical with Lead III.

4. The S-T and T segments tended to form a single, continuous element.

5. In the chest leads, as in the limb leads, in these cases of intraventricular block, the T wave showed a tendency to be directed opposite to the major or prolonged phase of QRS.

In addition, it was found that, when one viewed the entire series of chest leads in a case, there was a greater uniformity between cases than is apparent when any pair of chest leads is compared.

In the common type of intraventricular block the chest leads are characterized by large QRS deflections at many points; they are either of the V or \wedge type, or of the N or $|/|$ type, and in the latter have a tiny preliminary phase. W or M types of QRS either are not seen or appear in only one or two positions, but N or $|/|$ types, with the two phases of approximately equal amplitude, occur at a number of points. The contour resembles that of left ventricular preponderance, except that QRS is prolonged. In all the cases QRS was downward, or mainly so, in the fourth intercostal space in the posterior part of the left axilla. Elsewhere, the direction of QRS was more variable. It may be entirely upright when the QRS in Leads II and III is also upright (concordant type), or, as in Fig. 1, when QRS is up in Lead II. It may be entirely upright over the central part of the front of the chest in the fourth intercostal space, as in Fig. 2, or entirely downward throughout the upper chest. With this wide variety of contours, it is difficult to see how the semidirect lead concept developed by Wilson, et al.,⁴⁻⁶ can be held, for all of these varieties are considered by their school to indicate left bundle branch involvement. The variation is accounted for more readily by the field theory developed by us, as will be shown below.

The indeterminate and uncommon types of intraventricular block have smaller QRS amplitude, and, at many points, W- and M-shaped

*The chest leads shown are the inverted images of those recommended by the American Heart Association Committee on Precordial Leads.³ This is due to the fact that they were taken before the above recommendation was published.

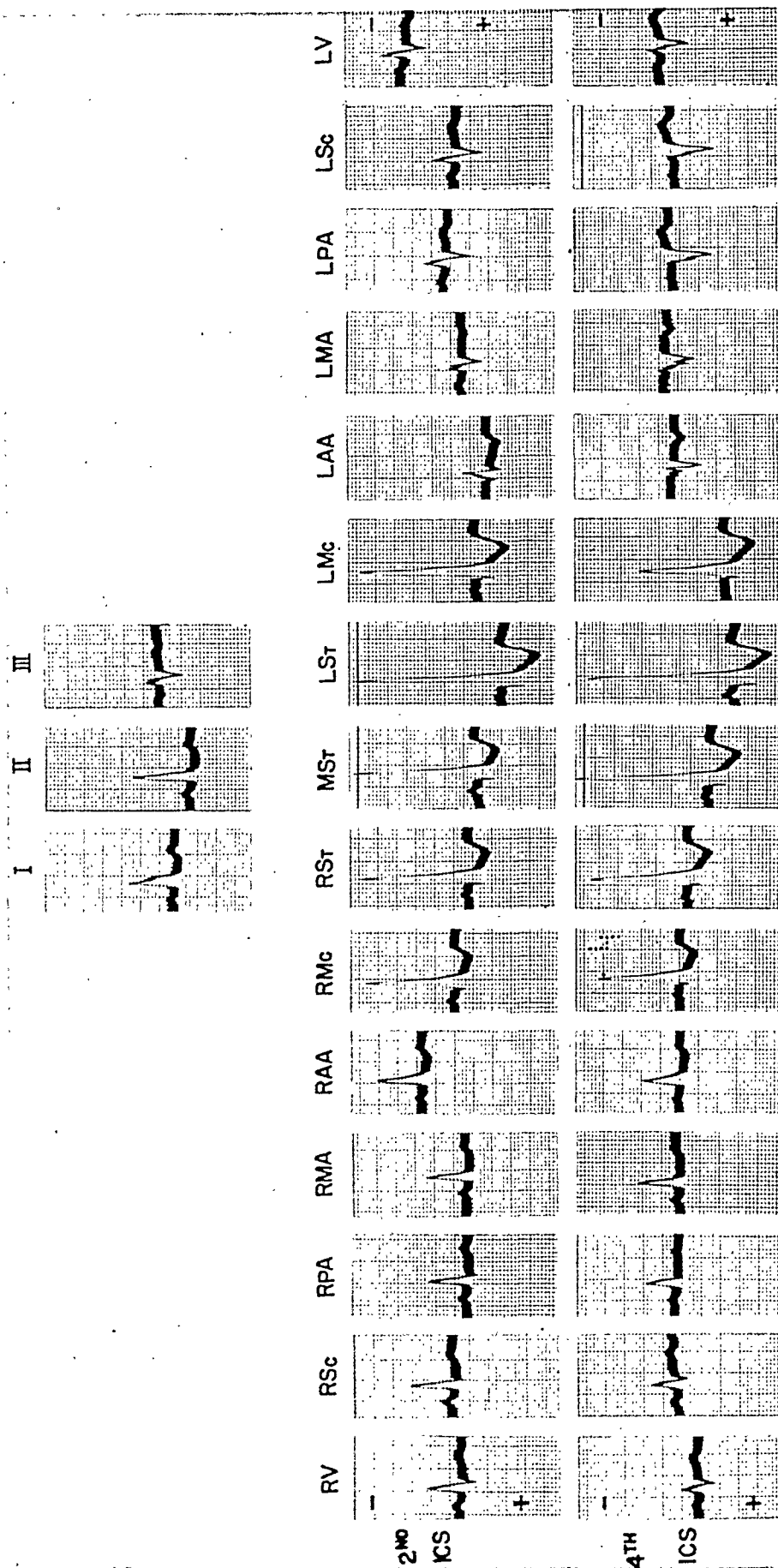


Fig. 1.—Electrocardiograms obtained on a patient with the common type of intraventricular block. In this and in Figs. 2 to 6 the standard limb leads, I, II, and III, are at the top of the figure; the middle row, labeled 2 ICS, indicates chest leads taken at the horizontal level of the second intercostal space at its junction with the sternum; the left leg was the distant electrode, and the exploring chest electrode was placed at the right paravertebral line (RV), the right scapular line (RSc), the right posterior, middle, and anterior axillary line (RPA, RMA, RAA), the right midclavicular line (RMc), the right parasternal line (RSt), the midsternal line (MSt), and at homologous points on the left side of the chest (LV, LSc, LPA, LMA, LAA, LMc, LSt); the lower row, labeled 4 ICS, indicates equivalent leads taken at the horizontal level of the fourth intercostal space at its junction with the sternum. The lead connections of the chest leads were the reverse of those recommended by the American Heart Association Committee. The curves are therefore inverted images of those obtained when the Committee's recommendation is followed, and are directly comparable with Leads II and III. The direction taken by the tracing when the polarity of the chest electrode becomes relatively negative and positive is shown by - and +. Discussed in text.

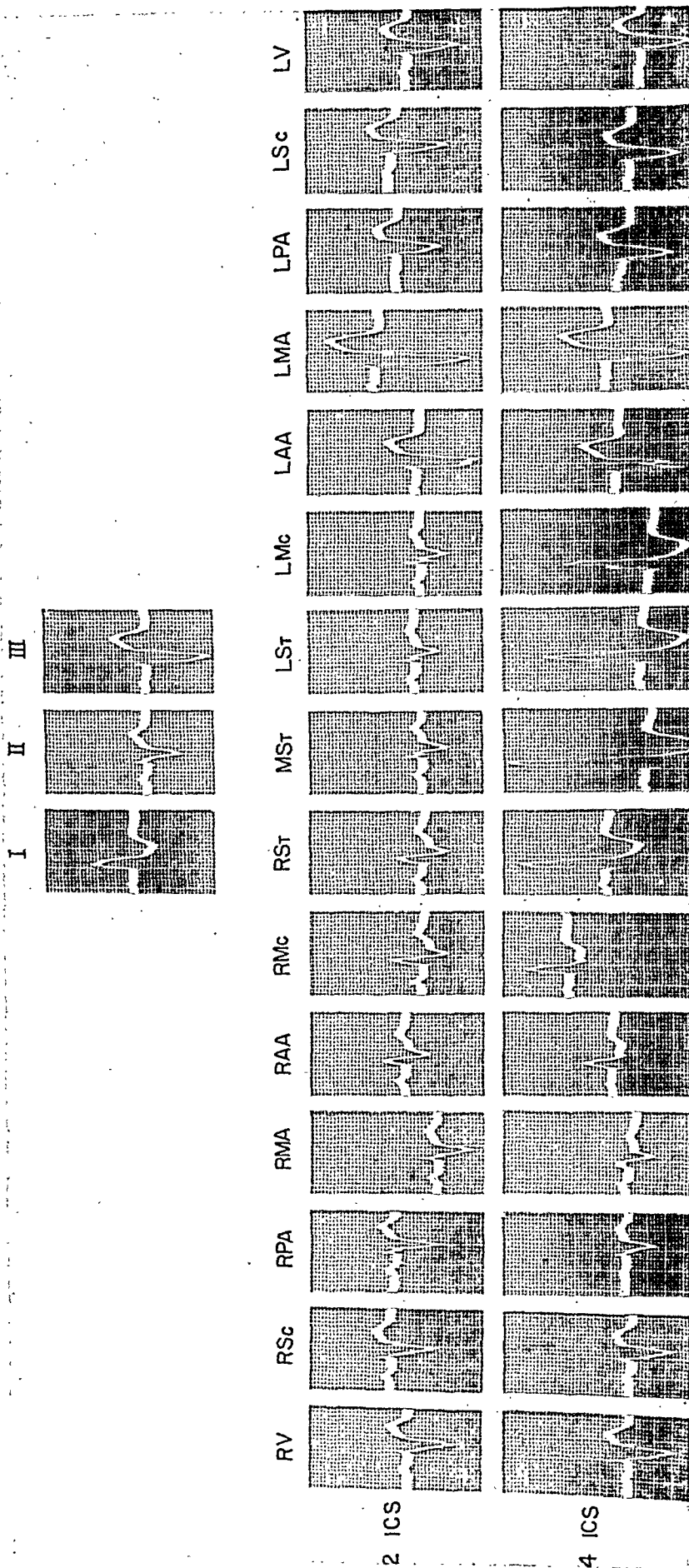


Fig. 2.—Electrocardiograms obtained on a patient with the common type of intraventricular block. Conventions as in Fig. 1. Discussed in text.

QRS complexes are seen. The former occur especially over a small region on the front of the chest in the fourth intercostal space, and have phases of about equal magnitude; no large V or \wedge types of QRS are found. In addition to the W type, N or $|/|$ types of QRS, in which only the second phase is prolonged, are seen at other points. This is especially frequent in the second indeterminate type (Figs. 3 and 4), and in the uncommon type (Fig. 5). In the first indeterminate type, large inverted QRS complexes of the M type are recorded from the left axilla, as in Fig. 6. This does not occur in the second indeterminate or uncommon form. These contours, again like those in the common form, are readily accounted for by the field theory developed below.

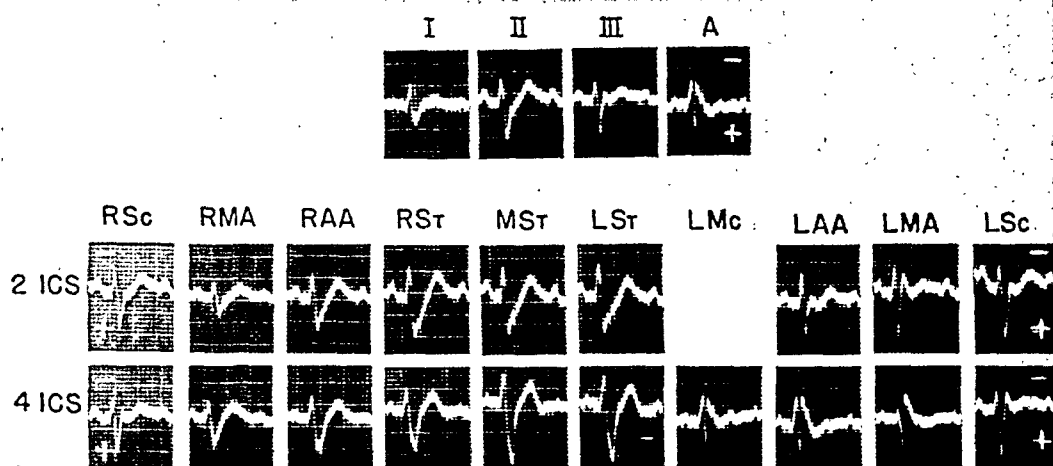


Fig. 3.—Electrocardiograms obtained on a patient with the second indeterminate type of intraventricular block. Conventions as in Fig. 1. A, in top row, is a lead with the chest electrode over the apex. Discussed in text. At autopsy this heart showed multiple infarcts.

It is thus apparent that intraventricular block can be distinguished in the chest leads in the same way as in the limb leads, and that, by studying both limb and chest leads, the type can be more clearly established than from limb leads alone.

The Distribution of Surface Potential as Ascertained From Chest Leads in the Various Patterns of Intraventricular Block.—In our previous communication² we pointed out that the chest leads gave information concerning the surface distribution of the electrical field created by the heart, and that this could be correlated with the character of the spread of the impulse and the spread of the restitution process through the heart chambers. The modifications caused by hypertrophy of the heart were shown to be in harmony with alterations in the mass and position of the heart, and did not require the assumption that any particular region of the heart determined the character of the deflections in any particular chest lead. This general conclusion is supported by the evidence obtained from the cases of intraventricular block reported here.

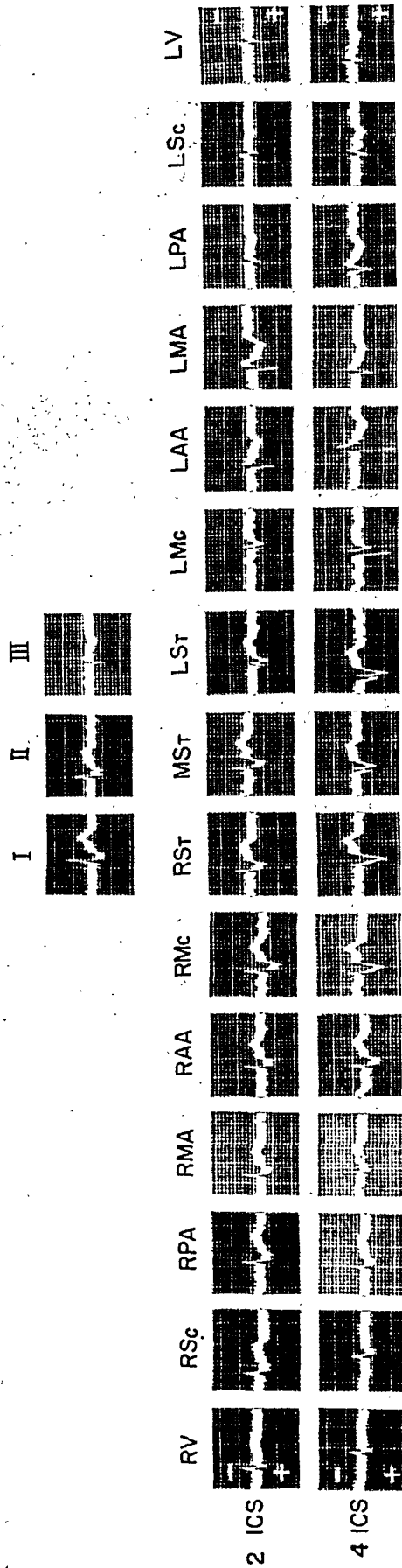


Fig. 4.—Electrocardiograms obtained on a patient with the second indeterminate type of intraventricular block. Conventions as in Fig. 1. Discussed in text.

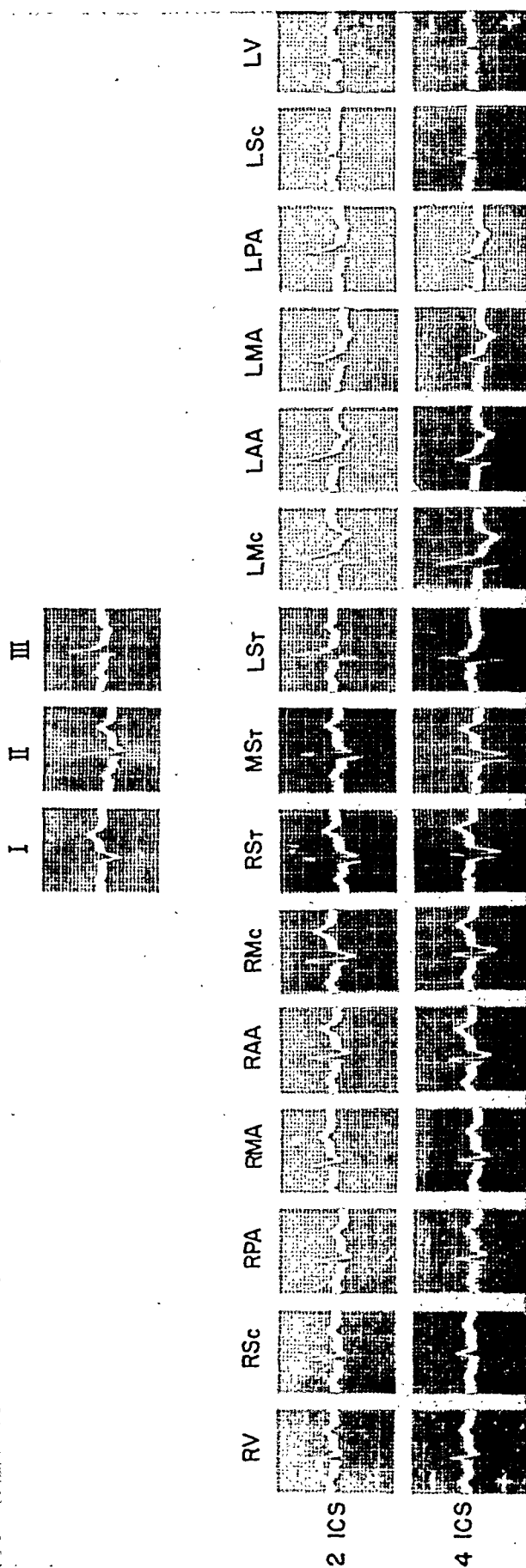


Fig. 5.—Electrocardiograms obtained on a patient with the uncommon type of intraventricular block. Conventions as in Fig. 1. Discussed in text.

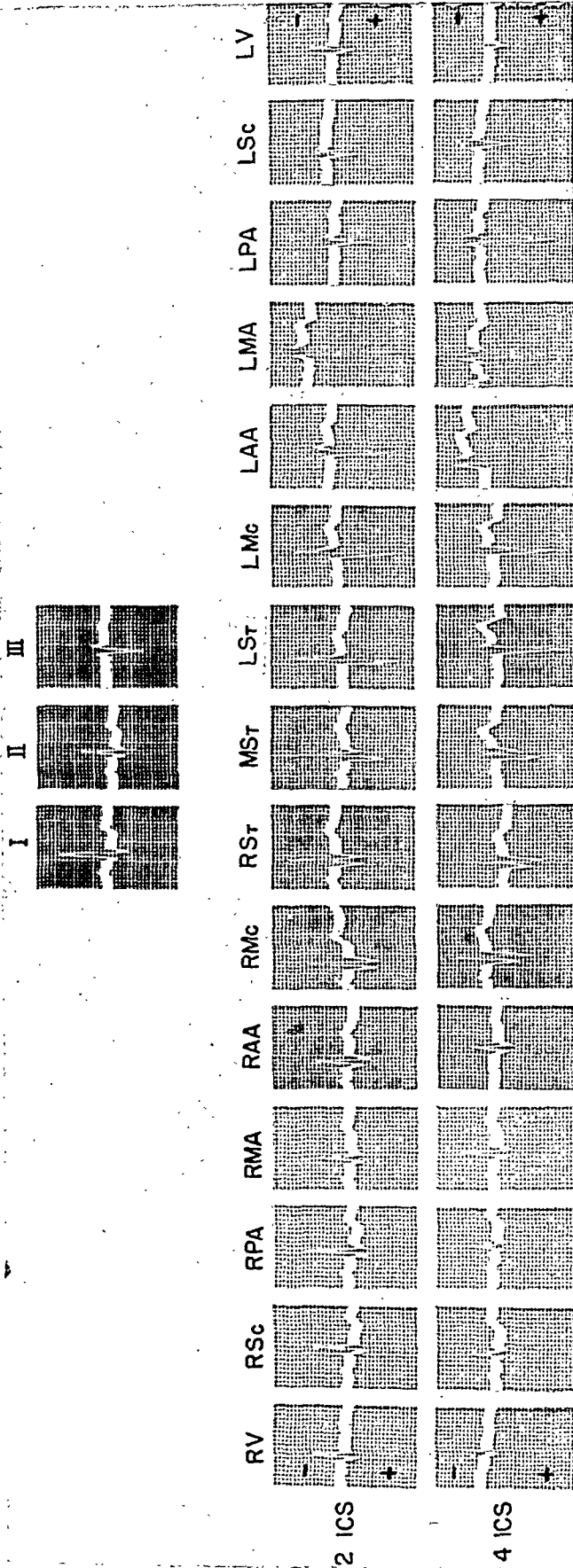


Fig. 6.—Electrocardiograms obtained on a patient with the first indeterminate type of intraventricular block. Conventions as in Fig. 1. Discussed in text.

The surface potential distribution at given instants of the heart cycle, namely, during the inscription of QRS and T, was measured in the manner described before, and the charts of the zero potential and of maximum negative and positive potential in the horizontal plane at the level of the fourth intercostal space were constructed in the same manner.

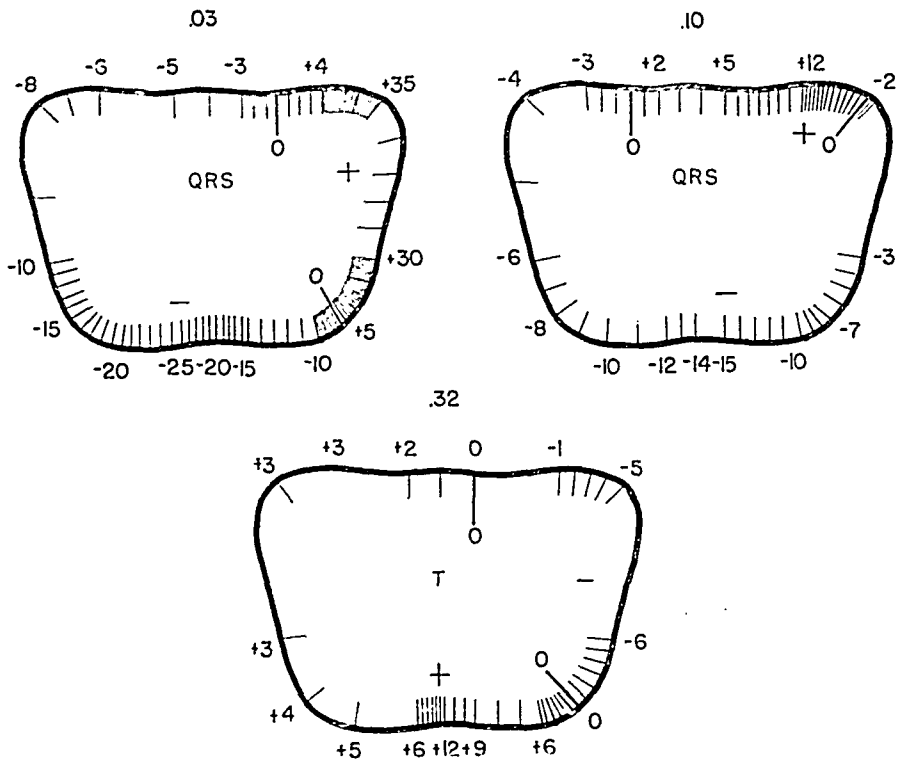


Fig. 7.—Cross-section diagrams representing the distribution of surface potential at the horizontal level of the sternal end of the fourth intercostal space in a case of the common type of intraventricular block (concordant variety). The several diagrams illustrate the state of affairs 0.03, 0.10, and 0.32 sec. after the onset of QRS; the first two are during the inscription of QRS, the last, during the inscription of T. Potential values are expressed in terms relative to leg potential, in multiples of 0.1 millivolt. The zero potentials are emphasized, and the maximum positive and negative potentials indicated. Discussed in text.

The same qualifications concerning quantitative accuracy, as previously stated, held here also. This is due to the fact (1) that absolute synchrony of the points of time selected in the various leads cannot be guaranteed, (2) that the leg ("indifferent") electrode is not at "zero" potential throughout the heart cycle, and (3) that neutralization of constant body current and injury currents from the heart before taking the record does not permit evaluation of the true potential levels at each point. Nevertheless, these inaccuracies do not nullify the value of the approach as a first, rough approximation, and do not militate against the deductions reached. The surface fields are shown in Figs. 7 to 13 for the patients whose electrocardiograms are illustrated in Figs. 1, 2, 4, 5, and 6, and for two whose electrocardiograms are not shown; of the latter, one was of the concordant upright type, and the other, of the common type, with QRS downward over the entire chest.

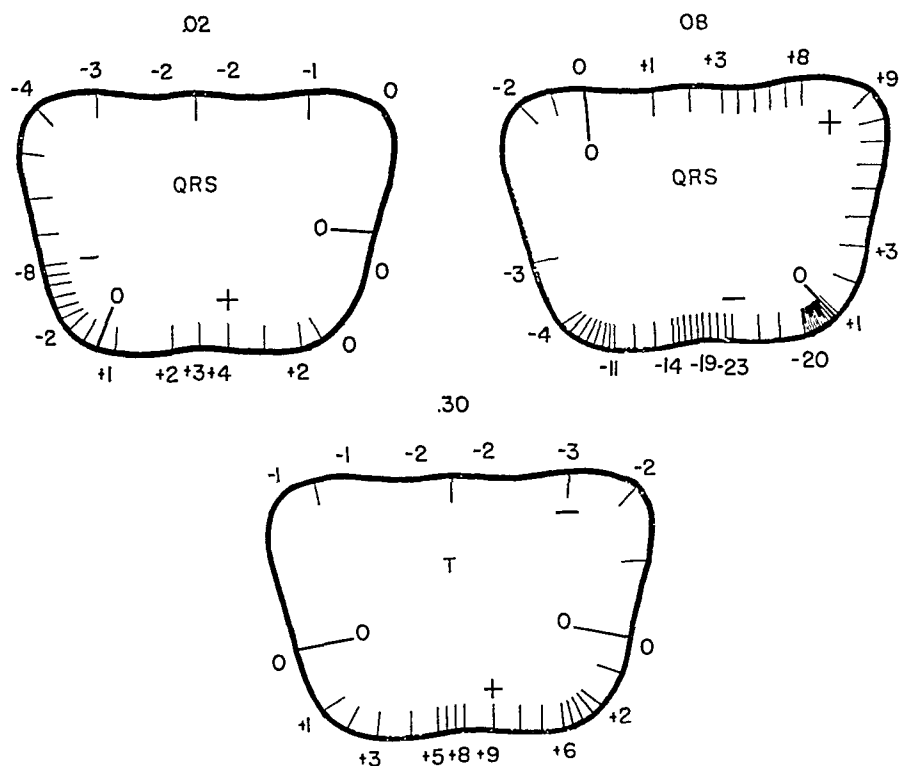


Fig. 8.—Cross-section diagrams representing the distribution of surface potential obtained as in Fig. 7 in a case (Fig. 1) of the common type of intraventricular block. The several diagrams illustrate the state of affairs 0.02 and 0.08 sec. (during QRS), and 0.30 sec. (during T) after the onset of QRS. Discussed in text.

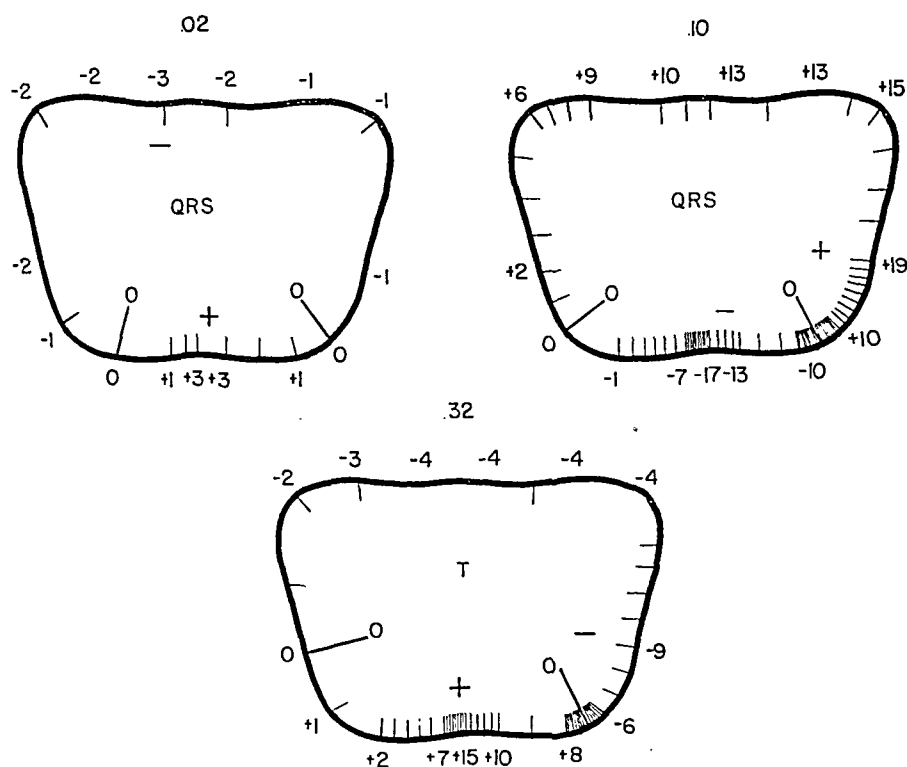


Fig. 9.—Cross-section diagrams representing the distribution of surface potential obtained as in Fig. 7 in a case (Fig. 2) of the common type of intraventricular block. The several diagrams illustrate the state of affairs 0.02, 0.10 (during QRS) and 0.32 sec. (during T) after the onset of QRS. Discussed in text.

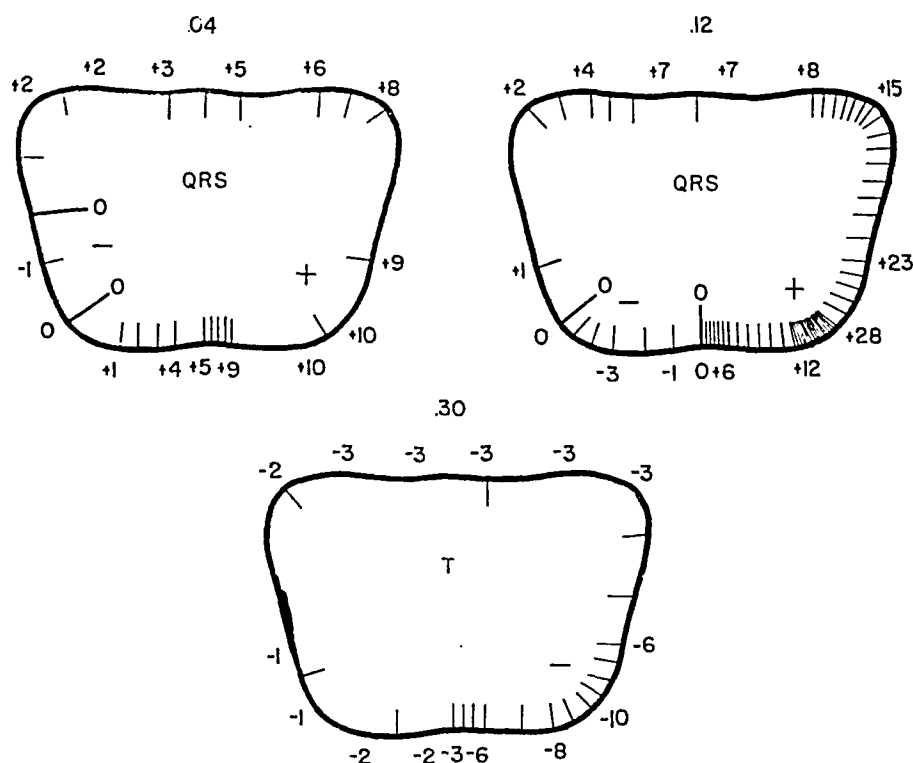


Fig. 10.—Cross-section diagrams representing the distribution of surface potential obtained as in Fig. 7 in another case of the common type of intraventricular block with QRS downward in the chest leads. The several diagrams illustrate the state of affairs 0.04, 0.12 (during QRS), and 0.30 sec. (during T) after the onset of QRS. Discussed in text.

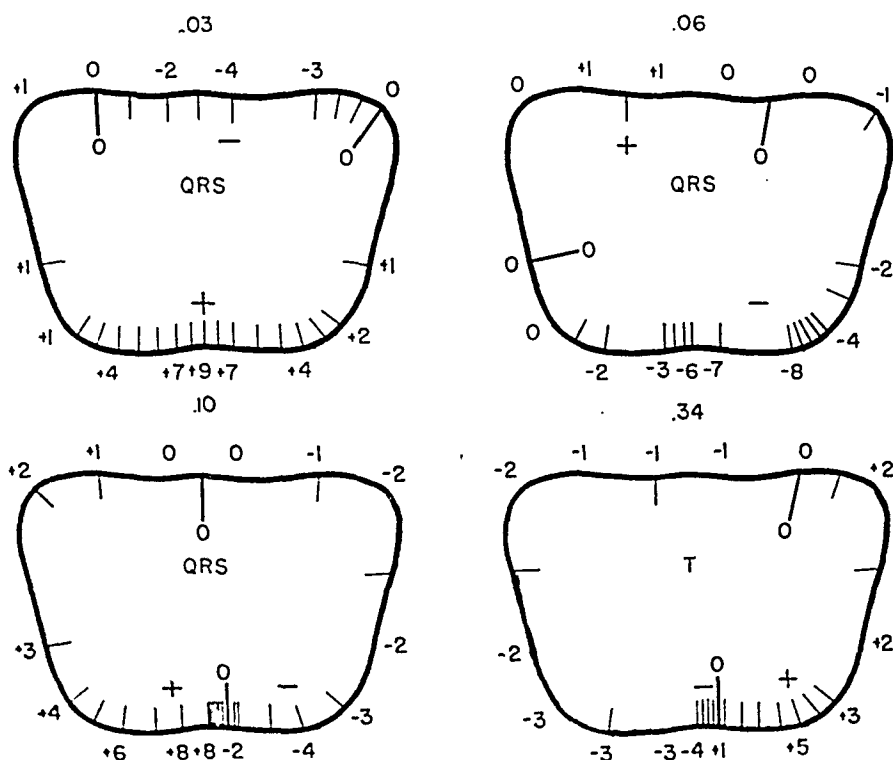


Fig. 11.—Cross-section diagrams representing the distribution of surface potential obtained as in Fig. 7 in a case (Fig. 5) of the uncommon type of intraventricular block. The several diagrams illustrate the state of affairs 0.03, 0.06, 0.10 (during QRS), and 0.34 sec. (during T) after the onset of QRS. Discussed in text.

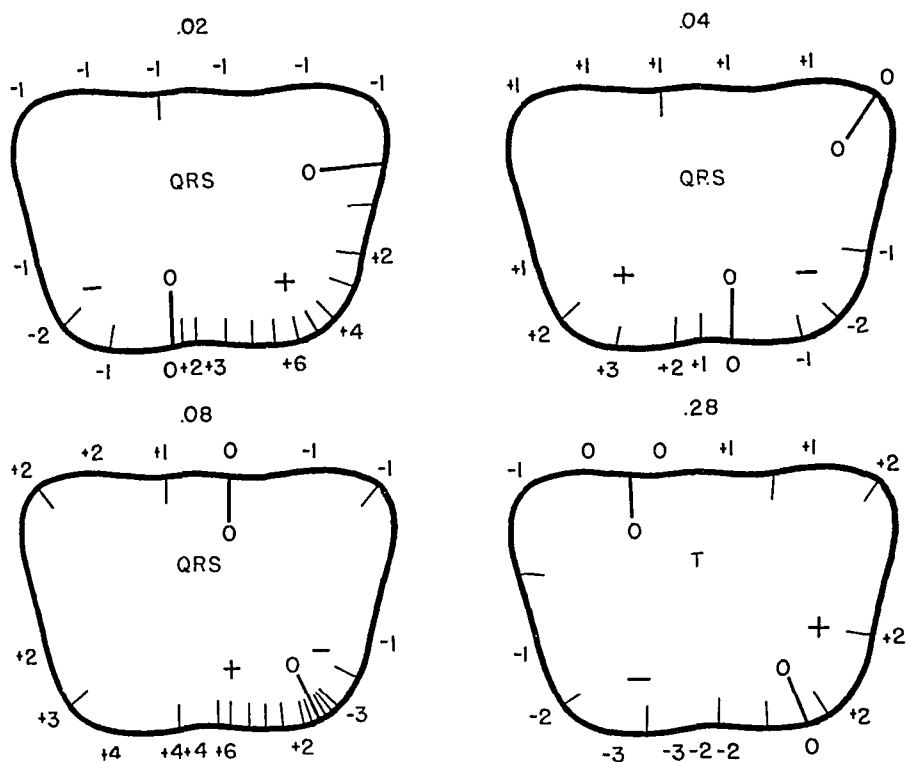


Fig. 12.—Cross-section diagrams representing the distribution of surface potential obtained as in Fig. 7 in a case (Fig. 4) of the second indeterminate type of intraventricular block. The several diagrams illustrate the state of affairs 0.02, 0.04, 0.08 (during QRS), and 0.28 sec. (during T) after the onset of QRS. Discussed in text.

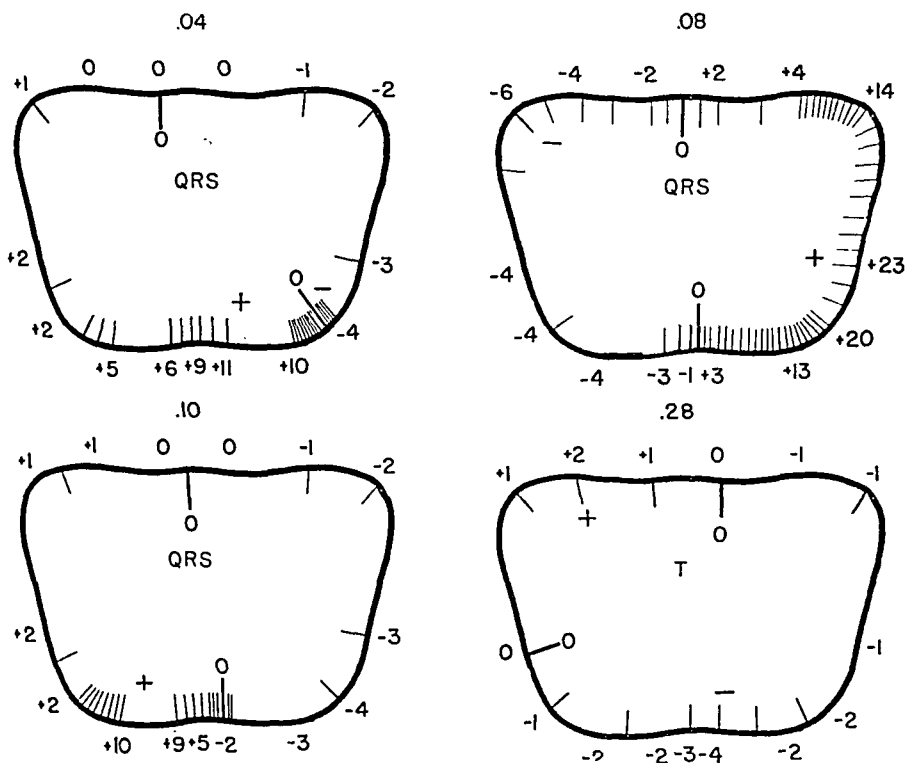


Fig. 13.—Cross-section diagrams representing the distribution of surface potential obtained as in Fig. 7 in a case (Fig. 6) of the first indeterminate type of intraventricular block. The several diagrams illustrate the state of affairs 0.04, 0.08, 0.10 (during QRS), and 0.28 sec. (during T) after the onset of QRS. Discussed in text.

In intraventricular block, as work from this department has shown, the effect of the block itself must be differentiated from the associated changes in heart contour, mass, and position.⁷⁻¹⁰ Both will influence the three dimensional character of the spread of the impulse and of the restitution processes which are responsible for the creation of the electrical field during QRS and T.

Variations in the field will thus be determined (1) by the location of the block or blocks, since more than one site may be involved, and these need not be precisely the same from heart to heart, and (2) by differences in the contour and position of the heart and the mass of its various chambers.

The chief difference between the common type of intraventricular block and the other varieties is the fact that the former has two phases in the development of the field during the spread of the impulse (QRS), and the latter have three. There are, in addition, striking differences in the direction of the field both during the spread of the impulse and during restitution. The differences will be more apparent after discussing the surface field in each type and subdivision of intraventricular block.

In the common type of intraventricular block there was a similarity of the surface fields in the four cases shown which is typical of the series; the differences are chiefly that zero lines vary in their initial position and rotate to different degrees in a clockwise direction when viewed from above, and that in one form (Fig. 10) the negative field seems to be located chiefly posteriorly, below the level of the fourth intercostal space. Further, the electrical field during inscription of the T wave is opposite in direction to that during the inscription of most of QRS. The field developed during the inscription of QRS in common intraventricular block resembles that in left ventricular preponderance, and so does that of the T wave, aside from the time constants. This would indicate that the spread through the left ventricle dominates the electrical field, and so lends support to the view that the block is chiefly, if not entirely, in the left ventricle. The restitution is such as to indicate a lag of recovery in the left ventricle, which would also support the view that the block was chiefly in the left ventricle.

The variations among these patients in the pattern of the fields is attributed, as mentioned above, to differences in the position of the heart, the relative hypertrophy of the two ventricles, and the exact location of the areas of block. Some clue as to the degree to which hypertrophy of the left ventricle determines the field can be obtained from a knowledge of the degree of hypertrophy present and from the amount of prolongation of the Q-E interval. The shorter the Q-E interval and the greater the left ventricular hypertrophy, the more must the deviation from normal in the field be ascribed to the hypertrophy.

Other influences, notably, loss of large masses of muscle as a result of disseminated, small and confluent, recent or healed infarcts will likewise play their role in altering the electrical field.

In the uncommon type of intraventricular block, the first two phases of QRS have fields similar to normal, but the third phase is so oriented as to indicate a delayed spread of the impulse through the right ventricle. This last is also true of the field during the inscription of the T wave. In short, only after the impulse has spread through most of the left ventricle does the dominance of the right ventricle become clear. Of course, the time at which this occurs would vary with other circumstances, as discussed above, but mostly with degree of hypertrophy of the right and left ventricles.

The close resemblance of the field in the second indeterminate type of intraventricular block to that in the uncommon type confirms the former's close relationship to the uncommon type of block, and supports the view that the two are of similar origin.

In the case of the first type of indeterminate block the conditions are more complex. In the first and third phases, the electrical field shows dominance of the right ventricle, but in the second phase this is not present, and, during the inscription of T, there is evidence of dominance of the left ventricle. This could be produced by any of three combinations, viz., (1) left ventricular preponderance, with block primarily in the path to or in the right ventricle, (2) right ventricular preponderance, with block primarily in the left ventricle, or (3) block involving both ventricles to an approximately equal degree. In these ways one could account for the varying dominance of the two ventricles on the electrical field. Examination of the heart for such hypertrophy, and the Q-E interval, would help to evaluate the presence of block in the left ventricle.

The evaluation obtained from such electrical field studies therefore lends support to the deduction arrived at from Q-E duration measurements in determining the location of intraventricular block.¹ In general, the deductions are in accord with those now established as a result of the work of Wilson and his school,⁴⁻⁶ but with some modification. Our results, however, although they lend support to the views concerning location of the block arrived at by Wilson, do not support his interpretation as to the meaning of the chest leads. The present study gives further evidence that the chest leads are not "semidirect" leads, as Wilson has argued, but rather depict, at a given point on the chest, the orderly alteration of the electrical field created by the passage of the impulse throughout the heart (and the restitution process), without the exertion of undue influence by the activity of the region of the heart beneath the electrode upon the potentials the latter records.

SUMMARY AND CONCLUSIONS

1. Intraventricular block is diagnosed in the electrocardiogram when the duration of QRS is 0.12 sec., or more, in the limb leads. It can be classified into four types, according to the electrocardiographic appearance, viz., the common, the uncommon, and the first and second indeterminate types. The chest leads in these groups fall into definite patterns.

2. The chest leads represent primarily the fluctuations in the electrical field of the region beneath the chest electrode during the spread of the impulse and during the restitution process throughout the heart. There is no reason to assume that there is dominance of any part of the heart over any other; all parts seem to play an approximately equal role in producing these electrical effects. The manner in which the impulse spreads and the restitution process occurs in the various regions of the heart appears to be the determining factor in establishing the electrical field.

3. These studies confirm and expand the views developed by us previously regarding the genesis of the electrocardiogram.

4. These studies confirm our observations in regard to the Q-E interval. They show that, although other influences, such as hypertrophy and displacement of the heart, as well as the causes which lead to low voltage, affect the appearance of the electrocardiogram in intraventricular block, the various types, by and large, appear to represent definite types of delay in the spread of the impulse, namely:

(a) The common type of intraventricular block appears to represent chiefly delay in the left ventricle.

(b) The uncommon and second indeterminate types of intraventricular block appear to represent chiefly delay in the right ventricle.

(c) The first indeterminate type of intraventricular block appears to represent a mixture of delay in the right and left ventricles.

We are indebted to several interns of the department for their assistance in obtaining the electrocardiograms.

REFERENCES

1. Bohning, A., Katz, L. N., and Langendorf, R.: Intraventricular Block. *AM. J. M. SC.* (in press).
2. Bohning, A., Katz, L. N., Robinow, M., and Gertz, G.: Value and Significance of Multiple Chest Leads in Man; Normal and Hypertrophied Hearts, *AM. HEART J.* 18: 25, 1939.
3. Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland: Standardization of Precordial Leads, *AM. HEART J.* 15: 107, 235, 1938. Also *J. A. M. A.* 110: 395, 681, 1938.
4. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle Branch Block, *AM. HEART J.* 7: 305, 1932.
5. Wilson, F. N., Johnson, F. D., Hill, I. G. W., Macleod, A. G., and Barker, P. S.: The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S Deflections in Lead I, *AM. HEART J.* 9: 459, 1934.

6. Wilson, F. N., Johnson, F. D., and Barker, P. S.: Electrocardiograms of an Unusual Type in Right Bundle Branch Block, *AM. HEART J.* 9: 472, 1934.
7. Katz, L. N.: Recent Advances in the Interpretation of the Electrocardiogram, *J. A. M. A.* 97: 1364, 1931.
8. Katz, L. N., and Ackerman, W.: The Effect of the Heart's Position on the Electrocardiographic Appearance of Ventricular Extrasystoles, *J. Clin. Investigation* 11: 1221, 1932.
9. Ackerman, W., and Katz, L. N.: Reversal in Direction of the Q-R-S Complex of Experimental Right Bundle Branch Block With Change in the Heart's Position, *AM. HEART J.* 8: 490, 1933.
10. Kissin, M., Ackerman, W., and Katz, L. N.: The Effect of the Heart's Position on the Electrocardiographic Appearance of Bundle Branch Block in Man, *Am. J. M. Sc.* 186: 721, 1933.

THE CHANGES IN THE FORM OF THE BEATING MAMMALIAN HEART, AS DEMONSTRATED BY HIGH-SPEED PHOTOGRAPHY

HOWARD B. BURCHELL,* M.D., AND M. B. VISSCHER, M.D.
MINNEAPOLIS, MINN.

IN 1939, Landis, Hunt, Moe, and Visscher¹ prepared a series of cinematographic films of the beating mammalian heart. The preparations photographed were the heart in situ, the heart-lung preparation, and the isolated heart. Although the films were prepared for general observation and study, it is believed that sufficient information was acquired to justify recording it permanently. Other investigators have used cinematographic records in the study of the heart movements, but in the present work ultra high-speed photography was the novel feature.

METHODS

The photography was done with three cameras; one had the usual speed of 24 frames in one second; another had a maximum speed of 600 frames in one second; and the third had a maximum speed of about 3,000 frames a second. If the films obtained from the latter cameras were projected at a speed of 15 frames per second, one observed a marked slowing effect on the cardiac movements. This effect, which may be called temporal magnification, would have maximum values of 40 and of 600 times. In the portion of the films which we have used for analysis, the moderately high-speed camera (called "super") took frames at an average rate of 100 per second, and the very high-speed camera (called "hyper") took frames at an average rate of 1,200 per second. A clock was photographed simultaneously, so that the interval between any two of the exposures could be ascertained accurately.

The interpretation of the films has been pursued in various ways. The longest time was spent in repeatedly reviewing the films on numerous occasions and noting phenomena as they appeared. The evidence based on these observations is the testimony of several witnesses who were in agreement. In regard to the heart shape and its changes, we have traced numerous consecutive frames on the reverse side of a transparent screen, and have had prints made of certain frames. These latter methods have supported our opinions in regard to heart shape which were obtained by direct observation.

Another method of study which contributed to the analysis of the cardiac motion was the tracing of the movement of reference points on the reverse side of a transparent screen while the projector was running. A second observer checked the exact time, by the clock shown on the film, as each point was marked. In this way the exact temporal relationships of movement of various points on the ventricular surfaces were obtained.

From the Department of Physiology, University of Minnesota.
Received for publication April 10, 1941.

*From the Mayo Clinic, Rochester, Minn.

THE SHAPE OF THE HEART IN SYSTOLE AND DIASTOLE

It will be readily recalled that, when the thoracic cage is opened, and particularly when the heart is removed therefrom, this organ loses the support of its semifluid environment and the influence of the negative intrathoracic pressure. The heart is then more subject to change in shape, and this shape distortion will be that of flattening. The latter will be functions of the intraventricular tension and myocardial elasticity. The isolated normal dog's heart, when in good condition, shows considerable flattening, particularly when its base and apex lie in a horizontal plane. In hearts suffering under a greatly increased load, very little flattening is seen. This has been interpreted as indicating that the diastolic volume has increased to a point where the ventricular wall cannot lengthen without considerable increases in intraventricular pressure.

Isolated Heart.

Minimal Aortic Pr. 85 mm. Hg.

Minimal Pulmonary Pr. 22 mm. Hg.

Output (Lt. Ventricle) 400 cc/min.

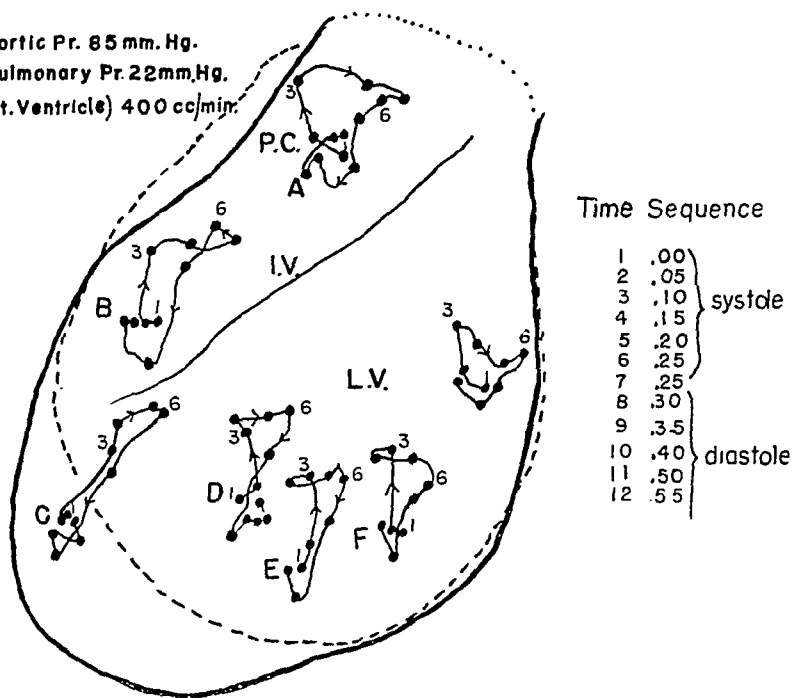


Fig. 1.—A ventral, inferior view of an isolated heart, showing the course of reference points on the epicardium during the cardiac cycle. Dots of the same number indicate synchronous positions in the spatial course of any reference point. To be particularly noted are the early lateral direction of point A (from 1-3), indicating early distension of the pulmonary conus, and the early marked movement of points B and C in the long axis of the heart, indicating a shortening of this axis. The various reference points are labeled A, B, C, D, E, F. PC, Pulmonary conus; IV, interventricular groove; LV, left ventricle. To avoid complication of the figure, only the synchronous positions 1, 3, and 6 are numbered. From these numbers the sequence of the dots from 1 to 13, with intervals representing 0.05 sec., can be readily followed. The line between any two dots, representing space over unit of time, is actually a measure of velocity, as well as of direction of movement.

The isolated heart, when lying on its side, will thus have the shape of a bulging cone flattened in its vertical diameter. With the onset of systole, the heart approximates a spherical shape very rapidly, and the gross

of a shortening of the long axis of the heart in early systole. Again, with reference to the course of the points on the left ventricle, it may be observed that the apex early in systole shows a torsion effect, with a slight rotation contraclockwise, followed, however, by a more marked rotation in the clockwise direction immediately before the onset of diastole. These movements can be demonstrated in Fig. 1 by joining points of the same number, which are isochronic. This type of consecutive rotation, which we have observed repeatedly, could be related to the superficial and deep musculospiral bundles of the heart, which lie roughly at right angles to one another.

In the tracing of point A (Fig. 1), the first part of the curve represents the distension of the pulmonary conus in early systole, which is readily seen on direct observation. The next part of the curve shows a rapid upward rise, due mostly to a rising of the whole heart, then a slight rotatory effect counterclockwise, followed by a clockwise rotation of the whole heart, as demonstrated by a movement of the reference point towards the right. In the tracings of points on the apex, the curves may be mainly in a vertical direction (Fig. 2). The slight, though definite, evidence of rotation in Heart No. 6 can probably be explained in part by the fact that these points are very close to the axis of rotation.

It will be readily appreciated that these figures represent movements of points in three dimensions, as projected on a frontal plane. This fact, together with slight indistinctness of the borders of the reference points and machine vibration, makes it impossible to obtain any very accurate measurements between any two points during the latter part of systole.

When the heart is distended, i.e., approaching its maximum diastolic volume, it maintains a roughly spherical shape throughout the whole cycle, and the movement of systole is to be made out with some difficulty. This slight movement is readily understood when one remembers that the ejected blood is changing the volume of a sphere which is a function of the cube of the radius. In such distended hearts we have been unable to observe apical rotation, and it is our belief that the "wringing-out" contraction occurs only at small systolic volumes.

SPECIAL CONSIDERATIONS REGARDING THE RIGHT VENTRICLE

This study has been illuminating with respect to the events which occur in the right side of the heart, particularly in regard to a differentiation of the right ventricle into inflow and outflow tracts, as emphasized anatomically by Kirch.² During systole, we have said that the ventricle approximates the shape of a sphere. Actually, the cavity of each ventricle would tend to assume a spherical shape, and, because of the higher pressure in the left ventricle, the systolic shape of the heart would be determined by the left ventricle, with the right ventricle acting as an

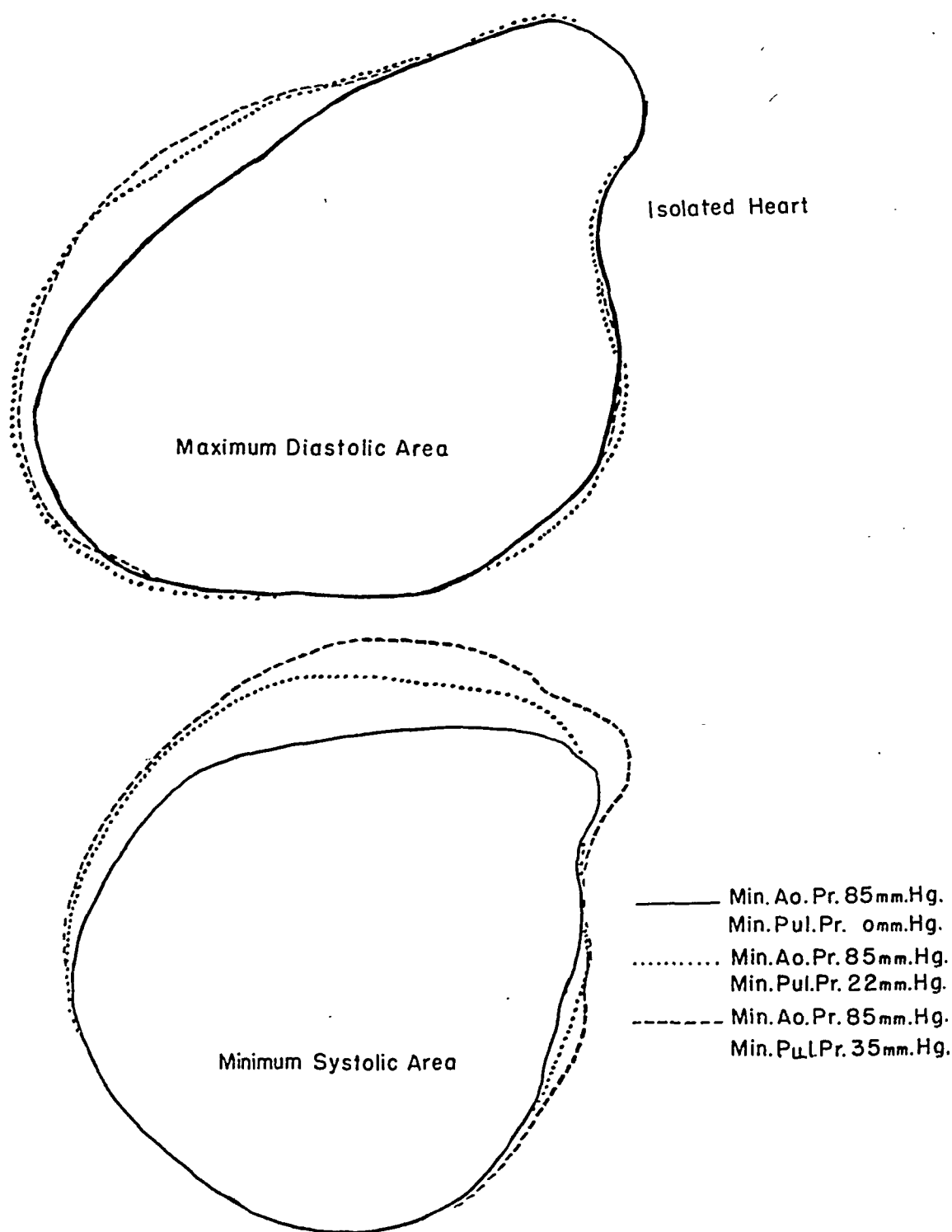


Fig. 3.—Figures obtained by tracings of the maximum diastolic and minimal systolic areas of an isolated heart. The areas are traced for three pulmonary pressures. It is to be noted that the diastolic shape remains about the same for the two higher pulmonary pressures. The flattened inferior aspect has been explained in the text. The heart rested on the table and was not otherwise supported. In all three systolic areas the close approximation to a circle is a noteworthy feature. With increases in pulmonary pressures there is an increasing distension of the pulmonary conus, or, more accurately, the outflow tract of the right ventricle.

appendage. This theoretical consideration is in agreement with our observations. It seems an unequivocal fact that the cavity of the lower and posterior portion of the right ventricle is reduced in volume because of the spherical shape assumed by the left ventricle in early systole, so that the right ventricular blood is stored during the isometric contraction and early systolic period in the pulmonary conus (Figs. 3 and 4).

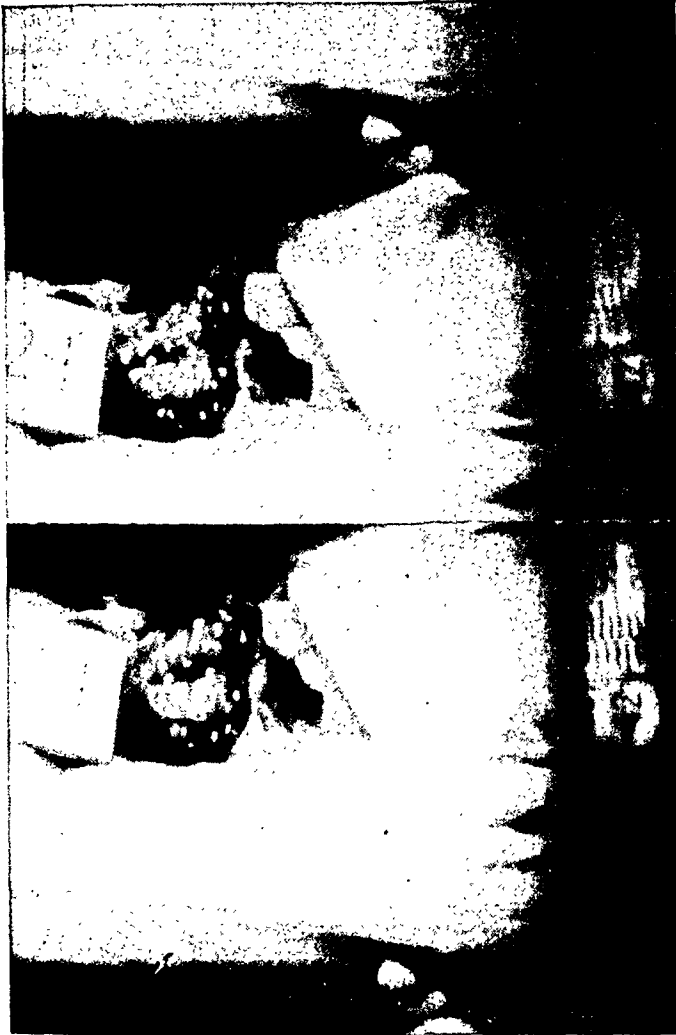


Fig. 4.—Reproductions of two photographic frames, showing the isolated heart at the end of diastole and 0.15 sec. later in mid-systole. The flattened shape of the heart and collapsed pulmonary conus are seen in the first photograph and the roughly spherical shape of the heart and distended pulmonary conus are seen in the second photograph. The movements of points on the surface of the heart were studied by following the displacement of the markers, which were small squares of white paper. The clock, marking hundredths of a second, is seen at the right of each frame.

With an increase in pulmonary blood pressure there is dilatation of the right ventricle in the region from the right ventricular apex to the pulmonary artery (outflow tract), which appears as a distended, tubular organ. These observations are in agreement with the idea expressed by Kirch, namely, that dilatation begins in the outflow tract of the right ventricle when this chamber is under continued strain.

SYSTOLIC AND DIASTOLIC WAVES IN THE PULMONARY CONUS

Observations on systolic and diastolic waves in the pulmonary conus have given further support to the idea that the inflow and outflow tracts of the right ventricle exist as separate functional units. There is a considerable difference in the degree of distension of the pulmonary conus in systole which is dependent upon the diastolic volume and pulmonary pressure.

In a rapidly beating heart, photographed in situ, we have seen that the pulmonary conus was little filled in diastole. Then, with the onset of systole, the pulmonary conus and pulmonary artery have acted as a continuous unit; what might be called a "bolus" of blood passed quickly from the right ventricular apex into the pulmonary artery. With this mechanism of emptying, there is an early, rapid, slight caudad movement of the heart, or "recoil." Colloquially we have referred to this phenomenon as a "pistol-shot" ejection.

Under conditions in which the pulmonary conus contains a considerable amount of blood we have noted an early, faint systolic wave which was propagated rapidly over the pulmonary conus to the pulmonary valves, and then reflected backward toward the apex. We are tempted to believe that this rarely observed wave indicates that inflow tract blood is entering the outflow tract, and that it is probably related to contraction of the *left* ventricle because the latter chamber early assumes a spherical shape.

During diastole, the pulmonary conus is the site of an interesting wave. With low pulmonary pressures the conus of the right ventricle may be totally collapsed at the onset of diastole, and a fluid wave is frequently seen to pass from the apex to semilunar valves and back again in the same manner as a fluid wave might travel in a collapsed bicycle tube. As this wave takes from 0.12 to 0.15 second for its complete journey, it travels fairly slowly, probably about 1 meter per second. This wave is believed to accompany some of the first blood which enters the right ventricle from the auricle, causing a wave to travel back and forth in the outflow tract before pressures are stabilized. This surging diastolic wave in the pulmonary conus is best seen with a temporal magnification of about eight times. Inasmuch as the wave appears mainly as a sequence of high lights and silhouette changes, it cannot be illustrated here. The possibility that such waves might be related to the physiologic third heart sound has been entertained. That this wave might be the cause of the diastolic vibration that Kountz and his co-workers³ have recorded seems a probability. The wave they described was usually of low frequency, without acoustic value, and occurred at the point occupied by the normal third heart sound, although the third heart sound might not be heard.

GENERAL COMMENT

There were several other phenomena that seem sufficiently interesting to record, although they only confirm what has been previously demonstrated in cardiac contraction. Following the administration of acetylcholine, the isolated heart showed periods of asystole lasting three to four seconds, and the first beat was manifested by a striking functional insufficiency of the tricuspid valve. The auricle became markedly distended with the ventricular contraction, and this could be correlated in time with the ventricular diminution in volume in its ejection period. This would indicate that, when there is prolonged asystole, the right auricle and ventricle form a common chamber and that the valve becomes insufficient as a result of the increased ventricular diastolic volume. We suspect that the marked venous pulse in the neck which is observed clinically with the returning cycle after an extrasystole, when the heart is beating slowly, is an analogous event.

After the administration of adrenalin, the increase in the force and rate of the cardiac contraction is readily followed. The upward stroke of the curves of the reference points is shortened in time, and the heart attains its spherical size so quickly that there is an "overshooting" due to the increased momentum, which produces a bouncing effect in the ordinary motion picture.

It has been shown by Viisscher⁴ that the partition of the coronary blood between coronary sinus and Thebesian drainage is a function of the aortic pulmonary pressure difference. It was suggested that increased pulmonary pressure played a nefarious role in right ventricular failure by interfering with the right ventricular blood supply, which is largely drained by the Thebesian system. The cinematographic records of the isolated heart show that distension of the right ventricle, produced by increments of pulmonary pressure, is improved by a later increase in aortic pressure. A quantitative study of this phenomenon has not been possible by this method of observation.

In a study of ventricular fibrillation high-speed photography did not contribute anything of exceptional interest. We have observed, however, that the onset of fibrillation may be characterized by undulatory movements of rather large masses of ventricular muscle. The later, finer, fibrillary movements and atonic phase, as described by Wiggers,⁵ are not readily discernible in our records.

Our evidence regarding the geometrical changes caused by cardiac contraction is in accord with that of Brednow.⁶ He also traced the course of reference points on the ventricular surfaces and noted particularly, as we have done, the shortening of the long axis of the heart. Our films were not taken with the view of correlating the cardiac output with the change between systolic and diastolic volumes. There are many

difficulties attendant on such calculations. Strughold⁷ has maintained that cinematography in one plane is an accurate method of estimating the stroke output of the heart. His pictures were taken from a superior aspect, so that, as the heart rose to a spherical shape, the peripheral outline would become smaller, independent of the output. Whether his correction, which was based on checking the camera-object distance, was adequate is somewhat questionable. With a suspended, isolated heart, we believe that cinematography, from a lateral direction, would give accurate figures for systolic and diastolic size but as a method for the measurement of cardiac output it would be by no means void of assumptions.

It was hoped that ultra high-speed photography might give us data on the finer details of ventricular events and rapid vibrations of the heart wall, but in this we were disappointed. We have noted A-V conduction time from the mechanical events, but one could not claim adequate accuracy for the figures obtained.

We are fully aware that the dog's heart differs from the human heart in that the pulmonary conus is relatively longer, and the apex is formed entirely by the left ventricle, but we do not believe that such differences would invalidate the application of our results, in a limited way, to the human heart. It is stated generally that there is a counterclockwise rotation of the heart, as viewed from the apex. Species differences are possible, but, for the dog's heart, we are certain that the greatest rotatory effect is clockwise. If our observations on the storage of right ventricular blood in the pulmonary conus during systole can be transferred to the human heart, it may explain the occasional roentgenkymographic observation of paradoxical systolic movement of the upper left border of the human heart.

SUMMARY

The mechanics of cardiac contraction, as studied by high-speed photography, have been described. The study has brought forth strong evidence that, although the gross movements of the ventricular wall are related to changes in form, the diminution in volume in systole is roughly a function of changes in spherical size. For the dog's heart, it has been shown that the greatest rotatory torsion movement is clockwise; that is, the right ventricle occupies a greater percentage of the anterior (ventral) aspect of the heart. In these experiments we obtained confirmatory evidence that the right ventricle is composed of two distinct units, namely, the inflow and the outflow tracts. An early diastolic wave over the pulmonary conus which is reflected back from the closed semilunar valves is seen with regularity.

REFERENCES

1. Landis, C., Hunt, W. A., Moe, S. K., and Visscher, M. B.: Color and Super Speed Cinematography of the Isolated Heart-Lung, *Am. J. Physiol.* 129: 400, 1940.

2. Kirch, E.: Pathogenese und Folgen der Dilatation und der Hypertrophie des Herzens, *Klin. Wchnschr.* 9: 769, 1930.
3. Kountz, W. B., Gilson, A. S., and Smith, J. R.: The Use of the Cathode Ray for Recording Heart Sounds and Vibrations, *AM. HEART J.* 20: 667, 1940.
Smith, J. R., Edwards, J. C., and Kountz, W. B.: The Use of the Cathode Ray for Recording Heart Sounds and Vibrations, *AM. HEART J.* 21: 228, 1941.
4. Visscher, M. B.: The Restriction of Coronary Flow as a General Factor in Heart Disease, *J. A. M. A.* 113: 988, 1939.
5. Wiggers, C. J.: The Mechanism and Nature of Ventricular Fibrillation, *AM. HEART J.* 20: 399, 1940.
6. Brednow, W.: Die Formveränderungen des schlagenden Herzens, *Ztschr. f. Kreislaufforsch.* 27: 401, 1935.
7. Strughold, H.: A Cinematographic Study of Systolic and Diastolic Heart Size, With Special Reference to Effects of Anoxemia, *Am. J. Physiol.* 94: 641, 1930.

THE ELECTROCARDIOGRAM IN INDUCED FEVER

PHILLIP T. KNIES, M.D.
COLUMBUS, OHIO

BECAUSE minor electrocardiographic changes have been observed in many common febrile diseases,¹ and marked alterations noted in malaria, pneumonia, and typhoid fever,²⁻⁴ similar changes might reasonably be expected with induced fever. However, the duration of natural fevers and their frequently nonremitting character are points of distinction from induced fever, and differences may therefore be expected in the respective electrocardiographic effects. For example, the prolonged auriculoventricular conduction time of natural malaria and the bradycardia of typhoid fever are uncommon in induced fever and may depend upon specific toxic effects of those infections.

Furthermore, although the effects of natural fevers upon cardiovascular physiology have been ascribed uncertainly to thermal, toxic, or mechanical factors, induced noninfectious fever affords an opportunity for critical evaluation of pure thermal change as it affects the pulse, blood pressure, cardiac output, blood flow, and electrocardiogram.^{1, 5-11} Clinical and experimental studies of the electrocardiogram in fever have appeared in the literature.

Influence of Thermal Changes Upon the Electrocardiogram of Animals.—Stimulation of the hearts of animals by the application of heat or cold to the exposed organ has resulted in electrocardiograms characteristic of the areas so stimulated, and in a shortening by heat and a lengthening by cold of electrical systole and diastole.^{12, 13}

In induced fever in animals, marked changes in the cardiac mechanism have been rare, though auriculoventricular block and ventricular rhythm have been described.² Negative P waves have become positive.² Shortening of the P-R¹⁴ and R-T⁹ intervals has been noted, and decrease in the amplitude of the QRS complex and notching of its deflections have been described.^{2, 9} T waves have been increased in height or inverted.⁴ Deepening of Q waves, disappearance of S waves, and S-T deviation from the isoelectric line have also been found. Some observers have noted changes which they were "accustomed to associate with coronary deficiency."⁴ In general, however, the effect of induced fever upon the animal electrocardiogram is surprisingly insignificant, at least until critically high temperatures are reached.

From the Department of Medicine, College of Medicine, Ohio State University, Columbus.

Received for publication March 8, 1941.

Furthermore, it is uncertain that these effects on animals, except those which follow the direct application of heat or cold, have been due entirely to thermal changes. For example, Cignolini has considered that the slight bradycardia and decreased systole noted in dogs during radio-induced fever may possibly be a specific effect of that form of energy upon the bundle of His and the adjacent sympathetic ganglia, independent of the heat induced.⁵

Influence of Fever Upon the Human Electrocardiogram.—The electrocardiographic effects of infectious, radio-induced, and diathermic hyperpyrexia have been studied in man. In general, these changes, also, have been of a relatively minor nature,^{6, 9, 15} or have been considered within the permissible limits of variation from the normal.⁷

All changes have been proportional to the degree of fever induced, reaching a maximum at its height and receding with it, although with some lag. Neyman¹⁶ has reported persistence of electrocardiographic changes for a few days after fever, but permanent alterations have rarely been found.⁹

The effects of malaria upon the electrocardiogram were studied by Mikawa, et al.,⁶ and by Weicker, et al.,¹¹ in twenty-five cases of neurosyphilis. Of the latter group, all but five patients had moderate to severe hypertension, and nine showed radiographic evidence of aortitis. This may account, in part, for the author's conclusion that therapeutic malaria is more dangerous than other forms of induced fever. Fatal occlusion of a coronary artery occurred in one case during the fourth chill, and, in several others, there were minor T-wave changes to which "a coronary significance" was attached.

Alterations of the electrocardiogram during short-wave radiotherapy were observed in twenty-four normal subjects and six cardiac patients by Domenighini and Grigolo,⁵ who used transthoracic radiation without permitting any rise in general body temperature. Alteration of skin conductivity caused by perspiration and peripheral vasodilatation was thus thought to be eliminated. No untoward reactions were observed, and it was concluded that at least some of the effects were due to a specific action of the radiation, apart from thermogenesis. However, the similar results obtained by Perinati (quoted by Domenighini⁵) with diathermy suggest that the common temperature increase may be more important than the particular form of energy employed.

Vesell and Bierman⁹ reported in detail the electrocardiographic changes during radiotherapy and diathermy in ten cases in which a fever of 104° to 106.5° F. was maintained three to five hours; they were unable to infer that any cardiac damage had been induced. Details of their observations will be discussed later in comparison with the present study.

We have found in the literature to date no analysis of the electrocardiographic alterations in fever induced in the air-conditioned cabinet of Kettering, which would presumably afford a clear view of the effects of pure thermal change upon cardiac electrophysiology.

Mechanisms operating to produce electrocardiographic changes in fever may include alterations in blood and tissue pH caused by varying carbon-dioxide and lactic acid concentrations.⁹ For example, alkalosis is at times encountered in fever therapy,¹⁵ and this has been shown by Barber, et al.,¹⁴ to be capable of producing deformity of the ventricular complex. Increase in metabolism and cardiac output, as well as peripheral vasodilatation⁹ and hemoconcentration, may also affect the electrocardiogram. Many of the electrocardiographic alterations observed in induced hyperpyrexia have been ascribed simply to a change in the heart rate, for they have occurred also during sinus tachycardia after exertion.

Electrocardiographic Alterations Previously Described.—Changes in rhythm, aside from tachycardia, have been infrequently noted and have usually involved a shift from an abnormal prefebrile rhythm to a normal one. Weicker, et al.,¹¹ reported the elimination of auricular extrasystoles for eight days after induced fever; auricular fibrillation, however, was unaffected.

The P-R interval is usually shortened in artificial fever, and Weicker, et al.,¹ found in only one instance the increased duration reputedly common in natural malaria; Mikawa, et al.,⁶ however, reported that the conduction time is generally prolonged after the chill.

An increase in the voltage of all component deflections of the electrocardiogram, and especially of the S wave, was also noted by Mikawa, et al. However, even though the S wave be considerably deepened, the sum of the R and S deflections has usually been found to be less during, than before, fever.^{5, 9} To this observation Domenighini and Grigolo⁵ attach an interesting interpretation. Considering the electrocardiogram as an index to the mechanics of cardiac action, they have assumed that a diminished sum of R and S in induced fever, without cardiac failure, signifies that the cardiac work has been accomplished by less than the previous expenditure of energy. This they attribute to improved coronary circulation or more efficient cardiac contraction, and upon these concepts they and Fianbaca explain their apparently favorable results after radiotherapy of the chest in angina pectoris.

T-wave alterations, variable in type and degree, have usually included a diminution in voltage. Weicker, et al.,¹¹ reported an instance in which a negative T₁, diphasic T₂ and isoelectric T₃ became up-right during fever. T₃ has been the most labile portion of the electrocardiogram, in the experience of all investigators.

METHOD

Six men and fourteen women, whose ages averaged 42 years, between extremes of 21 and 57, received from one to nine inductions of fever in the air-conditioned Kettering cabinet. Fifty-two such treatments were observed, making an average of two and one-half treatments per patient; the mean duration was four and one-half hours, between limits of two and one-half and ten hours. The treatment

was for arthritis in nine instances, for taboparesis in three, for other forms of syphilis in six, and for gonorrhea in one. All of the patients had been carefully examined before the induction of fever, and those who had cardiovascular disease, beyond minor arrhythmia or moderate hypertension, were eliminated.

The maximum prefebrile blood pressure of the group was 182/116 mm. Hg, which changed during fever to 128/86 mm. Hg; this was accompanied by small S-T alterations, but not by subjective complaints. The average change in blood pressure in the entire group during fever was a decrease of 24 mm. Hg, systolic, and of 12 mm. Hg, diastolic. A return to the original levels occurred quickly in all cases after the cessation of fever.

Records were made with a string galvanometer, and in each instance the standard leads were taken before the induction of fever, during its rise, at its height, and upon its subsidence; additional tracings were taken in many instances. The electrodes were reapplied before each tracing, and the standardization was checked before each section. Notable changes in the electrical resistance of the patients were seldom encountered.

RESULTS

Changes in Rhythm and Conduction.—Sinus tachycardia occurred in every instance; it was most marked during the induction of fever, with often a slight recession later, even though the fever had been maintained. As others have observed, the increase in heart rate was due principally to shortening of the T-P interval. In one case, recurrent ventricular escape was not observed after the first treatment; in another, multiple pacemakers disappeared during and immediately after fever, but later observations were not available. Numerous ventricular extrasystoles were eliminated in a third case during treatment, but returned later; this may have been due to a change in heart rate alone.

The P-R interval was usually found to be decreased in all leads by 0.02 to 0.04 second during fever; it returned rapidly to the original duration after the treatment, when it occasionally became 0.02 second longer than before fever. In every instance the original duration had been recovered before the next treatment. Similar observations were made by Vesell and Bierman,⁹ in whose series the maximum decrease was 0.05 second during fever.

These authors reported that the P waves were diminished by 0.01 to 0.02 second in duration, with a maximum change of 0.04 second, and that the QRS complex was shortened by a maximum of 0.04 second, but remained unaltered in some instances and increased in a few. Similar observations were made in the present series.

In no instance was the QRS complex sufficiently prolonged to indicate a serious intraventricular conduction defect.

Vesell and Bierman⁹ reported that the T wave was more often diminished than increased in duration, and that the ventricular, or R-T, section of the electrocardiogram in their series was shortened in all cases in Lead I, but increased in five of ten cases in Lead II or III, or both.

Such an analysis is rendered extremely difficult by the uncertainty of measurement and was not attempted in the present study.

Changes in Voltage.—Because of the fact that some patients received more treatments than others, changes in the deflections of the electrocardiograms were analyzed with respect to the number of cases in which they occurred, as well as to the number of treatments. This double analysis demonstrated that changes in any part of a tracing usually occurred consistently in all of the treatments of a given patient; there were, however, exceptions, particularly in the QRS complex and the T wave.

The P waves in all leads usually were increased in height during fever; the maximum increase was 2 mm., but some remained unchanged and a few became smaller. After fever, the deflection usually returned to its original height, and in several instances became even lower than before fever in Leads I and II; a post-febrile height greater than the original was commonly noted in Lead III. These observations are similar to those of Vesell and Bierman,⁹ in whose series, however, a greater proportion of records showed diminished height during fever.

The same authors noted one instance in which Q_3 was sufficiently large during fever to fulfill the criteria for "prominent or significant Q_3 ," but the usual Q-wave changes in the present group were less than 1 mm., and diminution in height was more common than increase in Leads I and II. Q_3 was usually deeper after fever than before it, but with a maximum difference of 1 mm. A return to the prefebrile contour was usually prompt, but in one instance Q_2 remained larger during the period of observation than it had been before treatment.

The R waves of all leads usually decreased in height during fever, but they recovered promptly, and this often began late in the treatment and continued after it; at times they became higher than before fever. A compensatory decrease frequently occurred after the occasional early increase in the height of R_1 . The maximum changes observed were 4 mm. in Lead I, 17 mm. in Lead II, and 7 mm. in Lead III. These alterations were not due to a change in the electrical axis; the latter appeared to be little affected by fever, as pointed out by Vesell and Bierman.⁹

These writers found that in several instances the height of the R deflection was less during fever than the normal minimum of 5 mm. but reported no slurring of the wave. The latter occurred in one case in the present series, and was associated with minor changes in the contour of the QRS complex and flattening of the T wave. During the next fever treatment of this patient, R_1 and R_2 were significantly slurred, and R_3 was completely obliterated. After both treatments the S-T₂ and S-T₃ segments remained slightly elevated temporarily, although the patient experienced no reaction suggestive of stenocardia. Later, fever did not produce such changes in this case. In the tracings

of another patient a slurred notch on the prefebrile S wave was displaced forward to a point near the apex of the R deflection during fever and moved back to its original position during recovery.

A deepening of S_1 occurred frequently during fever, but S_2 and S_3 were usually unaltered; the maximum change was 4 mm. in Lead III. Vesell and Bierman⁹ reported increased depth of the S wave in Leads I and III, and equal numbers of increases and decreases in Lead II, with a maximum change of 4.5 mm. in Lead III.

R was added to S to permit comparison with the observations and interpretations of Domenighini and Grigolo, as noted above. RS_2 and RS_3 were generally decreased, as stated by these authors, but RS_1 was usually increased. The maximum diminution of R plus S was 10 mm. in Lead III. In all leads these changes were usually overcompensated later, especially after fever. Thus, granting for the moment that a decrease in R plus S is an indication of greater cardiac efficiency during fever, the overcompensation after subsidence of the fever would indicate that there is a dangerous phase of cardiac inefficiency after hyperpyrexia.

In the present series the S-T segments of all leads remained almost uniformly isoelectric, and all deviations were less than 1 mm. Vesell and Bierman⁹ reported equally uniform depression of the S-T segment in Leads I and II and elevation in Lead III, but the changes were of the same order as in our cases.

The T wave in Lead I was usually decreased in height during fever, but later returned to, or exceeded, its original size. T_2 was increased and decreased equally often. T_3 was heightened by the majority of treatments, but decreased slightly in the majority of patients. The maximum changes were 3 mm. in T_1 , 1 mm. in T_2 , and 5.5 mm. in T_3 . The observations of Vesell and Bierman⁹ were not significantly different but included three instances in which a prefebrile inverted T wave in Lead III became upright during treatment. In our own group a change from plus 2 mm. to minus 3.5 mm. occurred once in Lead III, and less inversion was observed in four other instances. T_1 and T_2 were never found to be inverted during fever.

DISCUSSION

The present study adds to previous reports, especially that of Vesell and Bierman,⁹ a detailed analysis of fifty-two electrocardiograms which were recorded on twenty patients during the induction of fever in the air-conditioned hypertherm of Kettering. The observations correspond closely with those of others on the human and animal electrocardiogram during fever and demonstrate the consistently minor nature of the electrocardiographic changes. The latter observation suggests that fever has only a slight direct influence upon the electrical activity of the heart

and that extracardiac factors are important in the production of the cardiovascular changes which occur in natural fever.

CONCLUSIONS

1. The electrocardiographic changes during hyperpyrexia, induced in the air-conditioned cabinet of Kettering, were observed through fifty-two treatments of twenty patients.

2. These changes were usually insignificant, and quickly disappeared when the fever subsided. In many instances, a temporary overcompensation occurred in the late febrile, or postfebrile, period. No permanent changes in the electrocardiogram were noted.

3. In no instance in the present series of patients, all of whom had normal hearts, were changes characteristic of coronary insufficiency observed, and no cardiac damage appeared to have resulted, insofar as the electrocardiogram and clinical observation permitted judgment.

4. In view of the close correspondence of the observations in the present series with those previously noted when fever was induced in other ways, it would appear that the observed changes are the result of physiologic processes incidental to the temperature increase, without regard to the mode of its induction.

REFERENCES

1. Cheer, S. N.: Effects of High Temperatures on Heart and Circulation, *Am. J. Physiol.* 84: 587, 1928.
2. Browe, G. R.: The Heart in Typhoid Fever, *Canad. M. A. J.* 20: 606, 1929.
3. Chagras, P.: Electrocardiographic Changes in Typhoid Fever, *Compt. rend. Soc. de biol.* 106: 505, 1931.
4. Porter, W. B., and Bloom, N.: Heart in Typhoid Fever, *AM. HEART J.* 10: 793, 1935.
5. Domenighini, R., and Grigolo, C.: Action of Short Waves Upon the Heart, *Gior. med. d. Alto Adige* 9: 485, 1937.
6. Mikawa, T., Nemura, G., and Harada, N.: Electrocardiogram of Patients Inoculated With Malaria, *Acta scholae med. univ. imp. in Kioto* 11: 391, 1929.
7. Phillips, J.: Physical Methods of Fever Production From a Physiologic Viewpoint, *Arch. Phys. Therapy* 19: 473, 1939.
8. Roffo, A. E., and Taquini, A. C.: Electrocardiographic Changes Following the Application of Short Waves, *Rev. Soc. argent. de biol.* 10: 190, 1934.
9. Vesell, H., and Bierman, W.: The Electrocardiogram in Fever; Changes in Induced Hyperpyrexia, *Am. J. M. Sc.* 191: 484, 1936.
10. Wiggers, C. J., and Orias, O.: Circulatory Changes During Radiotherapy, *Am. J. Physiol.* 100: 614, 1932.
11. Weicker, B., and Kessler, M.: Induced Malaria and the Electrocardiogram, *Ztschr. f. Kreislaufforsch.* 30: 9, 1938.
12. Otto, H. L.: Action of Cold Upon T Waves of Electrocardiogram, *J. Lab. & Clin. Med.* 14: 718, 1929.
13. Smith, F. M.: Effects of Heat and Cold on Ventricles and T-Deflection of Electrocardiogram, *Heart* 10: 391, 1923.
14. Barker, P. S., Shrader, E. L., and Ronzoni, E.: Effects of Acidosis and Alkalosis on the Electrocardiogram, *J. A. M. A.* 106: 324, 1936.
15. Simpson, W. M.: Studies in the Physiology of Fever, *J. A. M. A.* 106: 246, 1936.
16. Neyman, C. A.: Artificial Fever Therapy, Springfield, Ill., 1938, Charles C Thomas, p. 44.
17. McGuigan, R. A.: Effect of Fever on Digitalis Action, *J. Lab. & Clin. Med.* 23: 999, 1938.

MYOCARDIAL DEGENERATION WITH HYPERTROPHY AND FAILURE OF UNKNOWN CAUSE

JOHN A. REISINGER, M.D., AND BASIL BLUMENTHAL, M.D.
WASHINGTON, D. C.

THE relationship of cardiac enlargement and heart failure to factors such as chronic valvular deformity and sustained hypertension, which require more work of the heart in order to maintain an adequate circulation, is well recognized. Although these causes for an increased cardiac load are present in a large percentage of patients with congestive heart failure, strain alone is not an entirely satisfactory explanation for the transition from compensation to decompensation without assuming some change in the status of the myocardium. This concept is not of recent origin, for William Stokes wrote, in 1854, "It was long ago observed by Laënnec that valvular diseases had but little influence on health when the muscular condition of the heart remained sound, and every day's experience confirms this observation." Many might consider this statement too dogmatic, but nevertheless would agree that the intrinsic integrity of the myocardium is the critical factor in cardiac function. Certainly, myocardial insufficiency occurs in the absence of valvular deformity or hypertension, and, even when causes for strain are existent, failure may be primarily due to depression of myocardial function by intoxications, infections, or metabolic disorders. Most often an inadequate coronary blood supply caused by coronary arteriosclerosis is responsible for the myocardial damage, although the possible noxious agents are numerous. It is frequently difficult to classify patients with myocardial insufficiency etiologically, and there is a tendency to assume, by exclusion, the presence of coronary arteriosclerosis in the absence of obvious causes for failure, particularly in middle-aged and older adults. Such reasoning will often give a correct diagnosis, but there is the inherent danger that the etiologic classification of coronary arteriosclerosis will be abused as much as the anatomic term, chronic myocarditis. It seems desirable to emphasize the possibility that cardiac enlargement and myocardial insufficiency may occur in the absence of the more common causes, and, in fact, in the absence of any discoverable cause. For this reason, and because of their interest, we have selected from 150

From the Cardiovascular Research Unit, Veterans' Administration, Washington, D. C.

Published with the permission of the Medical Director of the Veterans' Administration, who assumes no responsibility for the opinion expressed or the conclusions drawn by the authors.

Received for publication May 22, 1941.

autopsy examinations, made in the last two years, five cases in which there were degenerative changes in the myocardium without apparent cause. Four of the five patients were known to have syphilis, and the relation of this to the cardiac disease will be discussed.

REPORT OF CASES

CASE 1.—S. T. L., a 45-year-old negro barber, had been well until four years before admission to the hospital. As a young man he had been a professional athlete, and had continued to be very active until the onset of his illness. About April, 1935, he first noted fatigability and slight dyspnea on climbing steps. His weight gradually declined without obvious cause, and about eight months after the onset of symptoms he suddenly developed a severe attack of dyspnea, orthopnea, and cough, necessitating six weeks' confinement in bed. At that time he was told that he had "heart disease." He recovered from this acute attack, but the dyspnea on exertion became more incapacitating, and he entered a hospital about a year after the onset of symptoms. At that time he weighed only 170 pounds, which was forty pounds less than his previous weight. His heart was considerably enlarged, and there was evidence of pulmonary congestion. There were no murmurs or arrhythmia, and the blood pressure was 124/84. Electrocardiograms revealed a first-degree auriculoventricular block and intraventricular block. The blood cell count was normal except for 51 per cent lymphocytes in the differential leucocyte count. The blood Wassermann and Kahn reactions were negative, and the urine was normal. The patient remained ten weeks in the hospital and improved considerably on rest in bed and digitalis. After discharge his activity was limited, and he did fairly well for about three years, although climbing steps invariably caused breathlessness.

In the spring of 1939, however, exertional dyspnea became more severe, and, within a month, severe paroxysms of dyspnea, especially at night, forced the patient to come into the hospital again. He again showed evidences of pulmonary congestion, but no hepatic enlargement, ascites, or edema. The heart had increased in size; no murmurs were audible; the rhythm was normal; the sounds were distant; and the pulmonic second sound was louder than the aortic second sound. The blood pressure was 104/84. The electrocardiogram again showed first-degree auriculoventricular block and also left bundle branch block. The hemogram showed a persistent, relative lymphocytosis as high as 69 per cent.

The patient made very little improvement, and, since the shape of the heart suggested pericardial effusion with tamponade, paracentesis of the pericardium was undertaken. Only a small amount of bloody fluid was obtained. The patient's condition continued to become worse, and he died about four years after the onset of symptoms.

Autopsy.—The pericardium contained about 500 c.c. of unclotted fluid mixed with blood; the latter probably was the result of trauma to the heart during the paracentesis. The heart weighed 742 Gm., but the walls were stretched thin and cut with considerable resistance; the cut surface presented a grayish, glistening appearance. There were no gross lesions of the endocardium or valves, and no ante-mortem thrombus was present. The aorta retained its elasticity, was not dilated, and showed only a small amount of atheromatous change. No obstruction of the coronary ostia was present, and, except for scattered patches of intimal yellowing in the first part of the anterior descending artery, the coronary vessels were grossly normal. There was a hemorrhagic infarct in the lower lobe of the right lung which was of recent origin.

Histologic Examination.—The entire myocardium in the sections studied exhibited severe damage which became progressively more advanced from the epicardial to

the endocardial portions. Marked hypertrophy of the muscle fibers, with large distorted nuclei, many of which were granular or very basophilic, was evident in less seriously involved areas of the myocardium. The fibers themselves showed gradations of injury from hypochromatophilia, slight vacuolization, and transverse fracture, to complete disappearance. In large areas the muscle fibers appeared to have melted away, leaving a loosely packed interstitial tissue which contained only a few mononuclear cells and an occasional fibroblast. Even in portions in which muscle fibers remained, the interstitial spaces were very prominent, but contained only a scattering of lymphocytes and a rare eosinophile. Fibrosis was relatively limited throughout the sections.

The small blood vessels were engorged, and, in areas in which the muscle damage was most severe, small hemorrhages were seen in the interstitial tissues. In these locations in which the necrosis was severe, even the walls of the small blood vessels appeared vacuolated and disrupted.

Summary.—This patient exhibited evidences of cardiac enlargement and myocardial damage without hypertension, valvular disease, or evidence of coronary arteriosclerosis to account for the structural lesions. Myocardial insufficiency began four years before his death and was strikingly relieved for a period of approximately three years after bed rest and digitalization. The electrocardiograms showed intraventricular block on numerous occasions, which ultimately conformed to the left bundle branch pattern. The heart was hypertrophied and showed degenerative lesions without conspicuous cellular infiltration or fibrosis.

CASE 2.—J. T., a 43-year-old negro laborer, was first admitted to the hospital in 1937 for treatment of lobar pneumonia. He presented the classical signs of right upper lobe consolidation, and the acute phase of his illness terminated in seven days by crisis. During this examination no abnormality of the heart was noted; the size and shape were normal roentgenologically, and the blood pressure was 115/70. The blood Wassermann and Kahn reactions were strongly positive, and it was discovered that the patient had received antisyphilitic therapy in 1931. He remained in the hospital about two months, but further treatment of his syphilis was not considered advisable.

After his convalescence he worked as a delivery man for fourteen months, when he was again admitted to the hospital with congestive heart failure. One month previously, intramuscular injections of bismuth had been started, and, after the fourth treatment, he noticed the onset of cough, dyspnea on exertion, orthopnea, and edema of the ankles. At this time the heart was definitely enlarged; the rhythm was normal; the rate was 120; and there was a soft systolic murmur at the lower end of the sternum. The blood pressure was 128/104, and there were evidences of congestion in the lungs, liver, and lower extremities. Electrocardiograms showed left bundle branch block and ventricular premature contractions. The patient improved rapidly on rest in bed and digitalis, and was discharged from the hospital in five weeks.

In spite of greatly restricted activity, congestive heart failure promptly returned, so that hospitalization was required at the end of two months. The findings were essentially the same as on the previous admission. The blood pressure during the congestive stage was 124/96, but fell progressively with improvement to as low as 85/55. He again recovered promptly and was discharged after five weeks.

Upon return to his home, the dyspnea, orthopnea, and a "catching" pain about the left nipple soon required his readmission to the hospital. On this occasion his blood pressure was 114/90, the blood cell count was normal, the cardiothoracic ratio in the teleroentgenogram was 57 per cent, and the left bundle branch block was still manifest in the electrocardiogram. He again made a marked symptomatic

improvement which was repeated on three subsequent admissions until his eighth and final admission in May, 1940. At this time there were the usual signs of severe myocardial insufficiency, but he failed to respond to treatment and died about three months after admission.

Autopsy.—The heart weighed 510 Gm., and the left ventricle was greatly dilated. The wall of this chamber cut with some resistance, and at the apex there was an area of subendocardial fibrosis. All chambers contained "chicken-fat" clot. The valves were normal; there was no obstruction in the coronary arteries from the ostia to the smaller branches which admitted dissecting scissors. The aorta was not dilated, was normally elastic, and showed considerable atheromatosis in flat plaques, and also a moderate amount of longitudinal furrowing which suggested the possibility of syphilitic involvement.

Histologic Examination.—The muscle fibers were markedly hypertrophied, with very large, often pyknotic, nuclei. Areas with vacuolization, loss of striations, and transverse fracture were not uncommon, but the most profound damage was found in the subendocardium, where the degenerative changes were far advanced; the necrotic muscle was replaced in some areas by loosely packed connective tissue. There was very little cellular infiltration in the interstitial spaces, and only scattered small and large mononuclear leucocytes and fibroblasts were seen. None of these occurred in focal accumulations.

The small blood vessels in the muscle showed no encroachment upon their lumina, and the larger vessels in the epicardium were similarly unobstructed, although there was some thickening of the media. No perivascular cellular collections were seen in any of the sections, and small collections of lymphocytes in the subepicardium bore no relation to the blood vessels.

Summary.—This patient was first treated three years before his death for lobar pneumonia, at which time his heart was apparently normal. He was known to have syphilis, and his symptoms of myocardial insufficiency developed after the fourth of a series of intramuscular bismuth injections. He did not present any evidence of arterial hypertension or valvular disease, but there were marked cardiac enlargement, left bundle branch block, and myocardial insufficiency; from the latter he made unexpectedly good, although temporary, recoveries on six occasions over a period of sixteen months. The heart was hypertrophied, and showed areas of degeneration, particularly in the subendocardium.

CASE 3.—J. S., a 40-year-old white man, was admitted to the hospital Sept. 4, 1939, with congestive heart failure, and died thirty-six hours later. He had first been seen in an army hospital, in 1932, for the treatment of a penile lesion which contained spirochetes, as shown by dark-field examination. The extent of subsequent treatment is unknown. In July, 1934, he again received medical treatment because of an injured shoulder; at that time physical examination revealed no cardiac abnormality. The patient entered an army hospital in 1935, complaining of severe pharyngitis. The patient's heart was normal and the blood Wassermann and Kahn reactions were negative.

Early in April, 1937, the patient noted a dull, dragging sensation under the right costal margin. He entered a hospital, where he was found to have "cardiac enlargement and auricular fibrillation." No murmurs were audible, the Wassermann and Kahn reactions were still negative, and no etiologic diagnosis was made. The patient was discharged after one week.

Three months later he enrolled in the Civilian Conservation Corps, but developed "dyspnea on exertion and pain and tenderness in the region of the liver," for which he was admitted to the Walter Reed General Hospital Sept. 20, 1937. He was found to have the peripheral signs of moderate congestive heart failure, moderate cardiac enlargement, and auricular fibrillation. No murmurs were heard and

the blood pressure was 146/86. Fluoroscopic examination revealed "left ventricular enlargement without aortic dilatation." The blood and spinal fluid gave negative reactions to tests for syphilis. The basal metabolic rate was normal.

On rest in bed and digitalis, improvement was marked, and he left the hospital Dec. 17, 1937, but was forced to enter a Veterans' Administration Facility ten days later because he again developed heart failure. On this admission the cardiothoracic ratio was reported as 50 per cent, and the blood pressure as 130/85. The electrocardiogram showed no abnormality other than auricular fibrillation. He was discharged from the hospital in a fair state of compensation two months later.

The patient was not hospitalized again until September, 1939, when he was admitted to this Facility with severe failure. He was comatose, orthopneic, and cyanotic; the cervical veins were engorged and pulsating; the heart beat was totally irregular, with a rate of 150. No murmurs were heard; the liver was enlarged; and there was edema of the superficial tissues in dependent portions of the body. Treatment was without avail, and death occurred thirty-six hours after the patient entered the hospital.

Autopsy.—The heart was greatly enlarged in all diameters and weighed 658 Gm. Although the chambers were large, the ventricular walls were thickened and showed no gross evidence of fibrosis or myomalacia. There was no appreciable dilatation of the aorta, which revealed only slight atheromatous change and nothing characteristic of syphilis. All of the valves were normal. The coronary ostia were patent, and the arteries showed only a slight degree of atheromatous change in the larger radicles, without any reduction of luminal cross section. Two wedge-shaped, healed infarcts were present in the right kidney.

Histologic Examination.—The muscle fibers were enlarged, and showed areas of light staining, hyalinization, loss of transverse striation, attenuation, and fragmentation. In sections cut transversely, considerable vacuolization was revealed. The nuclei were swollen and palely staining, with granular chromatin.

Spreading of the muscle bundles, and, to a lesser extent, of the fibers, was conspicuous, and the interstitial collagen was more compact. Cells were not prominent in the interfascicular tissues except for occasional areas of fibrosis between fractured fibers, in which leucocytes and fibroblasts were somewhat increased. The venous channels were engorged with blood, but the arterioles did not appear to be significantly damaged; the only change was an increase in perivascular connective tissue. Interstitial hemorrhage was present, and hemosiderin formation indicated that it had occurred ante mortem. The endocardium was undamaged except for an inflammatory reaction beneath a small ante-mortem thrombus.

Summary.—A 40-year-old man gave a history of recurring myocardial insufficiency over a period of 2.5 years. He had auricular fibrillation, which probably was not treated properly during periods between hospitalizations, but there was no clinical evidence of persistent arterial hypertension, valvular disease, or coronary artery involvement. Although serologic examinations for syphilis were repeatedly negative, there was a record of a penile lesion which had been diagnosed as syphilitic by dark-field examination. The heart was hypertrophied and showed degeneration, with some increase in fibrosis, particularly about the blood vessels.

CASE 4.—W. B. H., a 53-year-old white man, died in this hospital during his fifth admission for myocardial insufficiency. He had previously been treated in two other hospitals for the same disability, which, he stated, was first manifested about six years before his death. On one occasion, when he was 15 years of age, a "leaking valve" was discovered during the course of a routine examination, but this apparently had not caused him any difficulty during his army service or in pursuing his occupation as a mechanic and chauffeur. As a young man he had had gonorrhea and a penile lesion, associated with buboes, for which he was given a

course of antisyphilitic therapy in spite of the fact that syphilis was never definitely established as the cause of the lesion. The blood Wassermann and Kahn reactions were repeatedly negative in this hospital. He had been married twice; a stillborn child resulted from the first marriage, and the second was without issue.

When he first entered the hospital, in 1936, his complaints were of moderate exertional dyspnea, palpitation, and slight evening edema of the ankles, all of which had been noted in the preceding three years. There was no clinical evidence of congestion; the heart was somewhat enlarged, particularly in the region of the pulmonary conus. Auricular fibrillation, with a ventricular rate between 50 and 60 and a pulse deficit of 10 beats per minute, was noted. No murmurs were heard, and the blood pressure was 98/56. The blood cell count and urine sediment were normal.

At the end of one week the patient was sufficiently improved to leave the hospital, and was able to maintain his cardiac compensation fairly well on proper doses of digitalis for about eighteen months, when he again entered the hospital because of increasing dyspnea. At this time there were a few râles at the bases of the lungs, and a soft systolic murmur was heard in the third intercostal space to the left of the sternum. The auricles were still fibrillating; the blood pressure was 96/72; the cardiothoracic ratio was 55 per cent; and the blood Wassermann and Kahn reactions were negative. After ten days of rest in bed he was again discharged.

Within five months the patient was again hospitalized, and there was slightly more evidence of congestive failure. Auricular fibrillation was still present, and the cardiothoracic ratio was 60 per cent. Within two weeks he had recovered sufficiently to be discharged.

Five months later he began to expectorate bright red blood, and, on admission to the hospital, his condition was essentially the same as on previous occasions except that there was evidence clinically and roentgenologically of consolidation at the base of the right lung. This was interpreted as a pulmonary infarct. Examiners thought that both a systolic and diastolic murmur were audible at the apex of the heart during this admission. His condition responded well to treatment; the heart rate dropped to 80 per minute, and the blood pressure rose from 88/60 to 100/68, but dyspnea on slight exertion persisted. He was allowed to return home under a physician's care.

A little less than six months later he entered the hospital for the last time, with slightly more marked congestive failure than on previous occasions. The heart rate was very rapid, a soft systolic murmur, but no diastolic murmur, was heard, and the blood pressure was 88/56. Digitalis was administered, and, in the course of a week, his heart rate had decreased to 60. He was improving satisfactorily when he suddenly became cyanotic and dyspneic and died within a few minutes.

Autopsy.—The heart was enlarged in all diameters, and weighed 538 Gm. There was a small area of fibrous adhesions between the pericardial layers at the base of the pulmonary artery, without evidence of pericarditis elsewhere. The wall of the left ventricle was thickened, although both ventricles appeared to be dilated. No mural thrombi were attached to the endocardium, which was smooth and intact throughout. All of the valves were competent, and the mitral valve, in particular, showed only atheromatous change of the aortic leaflet, without any deformity. The aorta was not dilated in its first portion and showed only moderate atherosclerosis with calcification. In addition, there was longitudinal furrowing, without conspicuous whitening of the intima, which did not strongly suggest syphilitic aortitis grossly. The coronary ostia, however, were above the commissural line, and the posterior orifice was lipped, causing some decrease in its size. The coronary arteries down to the smaller branches showed only a minimal amount of atheromatous change and no decrease in their lumens.

Histologic Examination.—The epicardium was thin, and showed the usual amount of fat. In the subserous tissue there were several collections of plasma cells and small lymphocytes which were unrelated to blood vessels. The medium-sized coronary arteries showed some eccentric intimal thickening and vacuolization of the media, but little else, and the arterioles exhibited no damage.

The myocardium showed hypertrophy, atrophy, and degeneration. In a layer three or four fibers thick, immediately beneath the subserous fat, the parenchyma of the muscle was exceedingly granular, and much of it was lost. No nuclei were seen, and the fibers were widely spread, but no hemorrhage or cellular infiltration was present. From this outer layer to the subendocardial layers, the muscle showed hypertrophy with secondary atrophy, sarcolytic degeneration, and widespread transverse fracture. The striations were fairly well preserved. There was a reduction in the number of muscle nuclei, which showed no uniformity in size, shape, or staining qualities. In the subendocardium there was another layer of muscle resembling that beneath the epicardium, but the necrosis was more widespread and severe. Even the blood vessels in this region showed destruction of the adventitia and media in places, with irregular fibrosis. Throughout the myocardium the interstitial spaces were very prominent, apparently because of edema, because many clear spaces were visible. There was no interstitial hemorrhage or accumulation of cells, and surprisingly little fibrosis was present, even in the areas which were most severely damaged.

Grossly and microscopically, the kidneys showed no unusual changes except congestion.

Summary.—A 53-year-old man gave a history of progressive myocardial insufficiency over a period of six years; it was markedly improved by periods of hospitalization, but terminated in sudden and rather unexpected death. He had had auricular fibrillation for at least four years, and was very irregular in his use of digitalis when out of the hospital. Although there was a history of a genital lesion, the diagnosis of syphilis was not definitely established, and it was thought most probable before the autopsy that rheumatic mitral stenosis was the cause of his cardiac disease. No signs, however, were ever consistently elicited which would justify a diagnosis of mitral stenosis, and no other cause for the auricular fibrillation, cardiac enlargement, and myocardial insufficiency was found. The heart showed hypertrophy and degeneration which was most conspicuous beneath the epicardium and endocardium. There was no evidence of valvular disease.

CASE 5.—J. G., a 50-year-old negro farm hand, was first admitted to the hospital April 2, 1937. He had been well until two years previously, when, shortly after the onset of an upper respiratory infection, he was awakened from sleep by a severe attack of breathlessness, cough, and wheezing that lasted all night. The following day his physician called the patient's attention to the fact that his feet and ankles were swollen. After a month's rest in bed the patient returned to work, and was able to do heavy farm labor without difficulty.

One year later (1936), again in association with a cold, the patient's dyspnea and edema returned, but disappeared after six weeks in bed, and the patient was able to return to heavy work about the farm.

Four weeks before the patient entered the hospital, in 1937, cough, dyspnea, edema, and palpitation were again noted, but, despite rest in bed and digitalis, he became progressively worse. Physical examination revealed marked orthopnea and impairment of the percussion note and breath sounds, as well as crepitant inspiratory râles, at the bases of both lungs. The heart was enlarged; the beating was totally irregular, with an apical rate of 110 per minute; and the heart sounds were distant and of poor quality, with accentuation of the second sound at the pulmonic

area. A soft systolic murmur was heard in the mitral area, and a similar murmur was audible at the base. Ascites and marked peripheral edema were noted. The blood pressure was 158/86.

The blood cell count was normal; the urine showed traces of albumin and hyaline casts which disappeared as the patient improved. On three occasions the blood Wassermann and Kahn reactions were strongly positive. An electrocardiogram showed auricular fibrillation, with frequent ectopic ventricular contractions. The cardiothoracic ratio was 64 per cent.

The patient improved rapidly with rest in bed and the administration of digitalis, so that, within a month, the signs of congestion in the lungs and superficial tissues had disappeared, although the liver was still enlarged. The blood pressure had dropped to 116/66, and sinus rhythm, with occasional ventricular premature contractions, had been restored. There was, however, partial auriculoventricular block, with a P-R interval between 0.20 and 0.30 second, and, in the chest lead, the primary QRS deflection was downward. Improvement was continuous, and, at the end of two months, the patient was discharged entirely free of symptoms and without evidence of congestive failure, although the heart was considerably enlarged.

Six weeks later the patient suffered exposure during a rain storm while watching a ball game, and shortly thereafter had symptoms and signs of failure again, probably as the result of a respiratory infection and the exertion of hurrying home. On admission to the hospital at this time there was a pleural effusion on the right side, in addition to pulmonary congestion and edema of the legs. The heart rhythm was of sinus origin, with occasional ventricular premature contractions and an auriculoventricular conduction time at the upper limit of normal (0.20 second). There were no other definite abnormalities in the electrocardiogram except a low-voltage, W-shaped QRS complex in Lead I which was not prolonged. Again the patient improved rapidly, and in one month's time was allowed to leave the hospital.

Soon after returning home he was forced to assume the responsibilities of his family because of his wife's illness, and the previous symptoms of failure promptly returned. It became necessary for him to re-enter the hospital only twenty days after his discharge. At this time the situation was the same as before, with pulmonary congestion, edema, a large heart, sinus rhythm, a systolic murmur, and normal blood pressure. The auriculoventricular block previously noted was absent (P-R interval 0.16 second), but the voltage of the QRS complexes and T waves was low. The cardiothoracic ratio was 68 per cent, and the differential leucocyte count showed 42 per cent lymphocytes.

The patient improved gradually, but, during this stay in the hospital, electrocardiograms revealed a recurrence of the auriculoventricular block, at times with complete dissociation; in some instances the rhythm appeared to arise in the junctional tissues, for normal P waves could not be identified. Although this man's symptoms and signs were largely relieved, he was advised against leaving the hospital because his exertion was too great at home. The patient discharged himself, against advice, but within a month had to re-enter the hospital for the fourth time because of marked congestive failure. After two weeks of rest in bed, however, the symptoms were completely relieved, and all signs of congestion, except the enlargement of the liver, had disappeared. Electrocardiograms taken during this period showed variable rhythms and particularly marked depression of the sinus pacemaker, so that ventricular escape occurred. This apparently was not due to digitalis.

The patient was hospitalized in another institution for congestive heart failure about one month after leaving this Facility. He manifested the usual prompt improvement on the hospital regime, but quickly developed failure again at home,

and was admitted to this hospital for the last time in July, 1938. In spite of the severe failure the heart rate was only 62, and, in the electrocardiogram, no P waves could be recognized; the QRS complexes were of low voltage of supraventricular origin except for occasional ectopic ventricular beats.

This time the patient did not respond to treatment, and died about three years after the first onset of symptoms. A few days before death an area of consolidation was discovered in the mid-portion of the right lung; this was thought to be infarction or pneumonia.

Autopsy.—The heart was markedly enlarged in all diameters; it weighed 533 Gm., and the pericardial sac contained about 100 c.c. of deep-yellow-colored fluid. The ventricular walls were thin, firm, and seemed fibrous when cut. An ante-mortem thrombus was enmeshed in the columnae carneae of the left ventricle.

The aortic valve cusps were not deformed, but the commissures were somewhat widened and the margins adjacent to the aorta slightly bound down, so that the valve pocket was smaller than usual. Although a water test was not done, it was assumed that this valve was competent, for a diastolic murmur was never heard, and the valve cusps seemed adequate to close the orifice, which was not widened. The other valves were normal.

The aorta in its first part was dilated and relatively inelastic. The surface was roughened by raised atheromatous plaques, furrowing, and an occasional, depressed, whitish scar suggestive of syphilitic aortitis. There was no obstruction of the coronary ostia, and the arteries showed only a minimal amount of flat atheromatous change, without any obstruction.

In the right kidney there were two areas of healed infarction, and in the upper lobe of the right lung there was a recent hemorrhagic infarct.

Histologic Examination.—The muscle fibers were for the most part enlarged, but many showed secondary atrophy, necrosis, and fibrous tissue replacement. The striations were distinct, although many of the enlarged fibers stained poorly and were vacuolated and fractured. The muscle nuclei were enlarged, with blunted ends. Interstitial spaces were prominent, and the entire connective tissue supporting structure of the heart was accentuated. Throughout the ventricular wall there were small, localized areas of muscle damage and fibrosis in which only a few scattered erythrocytes were seen; leucocytes, plasma cells, and fibroblasts were conspicuously scarce. In the older areas of damage, fibrosis was complete, and this was particularly true in the subendocardium, where the damage had been most severe.

The larger coronary arteries showed some intimal thickening which did not significantly encroach upon the lumens, and the smaller vessels were thin walled, with a slight increase of perivascular connective tissue, but no other cellular elements.

Beneath the partially organized thrombus on the endocardial surface there was a definite leucocytic and fibroblastic infiltration.

Summary.—A 50-year-old negro farm laborer had eight attacks of myocardial insufficiency, with congestion, in the three years before his death. These began originally with an attack simulating bronchial asthma, but subsequent events did not seem to confirm the original impression that the heart failure was primarily the result of pulmonary hypertension. None of the other common causes of heart strain, such as arterial hypertension and valvular disease, were present to account for the marked cardiac enlargement and myocardial insufficiency. It was thought that this case might be one of syphilitic myocarditis, although the surprising recuperative power of the heart seemed incompatible with the usual conceptions of this disease. The heart was enlarged, and there were areas of muscle damage and fibrosis throughout the myocardium.

COMMENT

These five patients were men between the ages of 40 and 53 years. Two were white and three were negroes, but, in proportion to their representation in the hospital population, the preponderance of colored patients in this group is more than three to two. The clinical manifestations were varied, although all had recurring attacks of congestive heart failure over periods lasting from 22 months to 6 years. Three had auricular fibrillation at some time during their illness, and one had it consistently; two showed the characteristic pattern of left bundle branch block (new nomenclature) in their electrocardiograms, and two had partial auriculoventricular block. A relative and absolute increase in the number of lymphocytes and large mononuclear cells was noted in the differential leucocyte counts of two patients, and in two of the five cases a pulmonary infarct was diagnosed, one before death and the other at autopsy.

These patients are grouped together, however, because each exhibited cardiac enlargement, with myocardial damage and insufficiency, for which no adequate cause could be found. At autopsy no congenital defects, dynamically significant valvular deformities, or coronary occlusions were demonstrated, and the moderate elevation of the diastolic blood pressure exhibited by some during periods of failure was not considered evidence of a chronic hypertensive state. In the past¹ it has often been assumed that, when cardiac hypertrophy is found at autopsy, it is due to arterial hypertension, providing other causes are not apparent, and even when evidence is lacking that the blood pressure was ever elevated. Our patients did not have more than moderate elevation of their diastolic pressures during their illnesses, and this returned to levels below the usually accepted upper limits of normal when compensation was regained. Furthermore, none of these patients had any significant degree of the renal arteriolar sclerosis or arteriosclerosis which is observed² in a high percentage of cases of persistent arterial hypertension of sufficient severity to cause heart failure and death. Cardiac hypertrophy and congestive failure, in the absence of hypertension or any obvious cause, have also been reported by others.³ None of our patients presented any clinical signs or symptoms suggestive of hyperthyroidism, severe anemia, metabolic disorders, or avitaminosis, and the pathologic examinations failed to reveal any definite clues as to etiology. Hypertrophy of the ventricles, as indicated by increased heart weight and enlargement of the muscle fibers, was present in all cases, and apparently occurred in the absence of the usual factors that increase the load against which the heart must work. Since sections from both ventricles were not routinely studied, it cannot be stated, except in one case, that both the right and left ventricles were hypertrophied. In addition to the hypertrophy, a widening of the tissue spaces was generally con-

spicuous and was perhaps due to interstitial edema. These spaces were usually clear, occasionally with some increase in the density of the ground substance; less commonly they contained a loose fibrillar network. There was some increase in perivascular fibrosis, but very little interstitial fibrosis except in one case, in which it was both diffuse and extensive in the walls of all chambers. For the most part the severely damaged portions of the myocardium showed little fibrosis.

In the sections studied, cellular infiltration was not prominent. There were a few clusters of cells not related to blood vessels in the epicardium of several hearts; there were collections of small round cells beneath ante-mortem thrombi on the endocardium in two cases and about a blood vessel in another, but otherwise only scattered, small groups of mononuclear leucocytes, plasma cells, and fibroblasts were seen. Two hearts showed areas of interstitial hemorrhage and collections of hemosiderin pigment which were easily accounted for by the damaged arterioles.

The most important microscopic change observed in all cases was degeneration of the muscle, which, however, varied considerably from heart to heart in character, extent, and severity. In four of the five cases the most marked damage was in the subendocardial region, although it was not limited to this area. In one case there was a layer of necrosis beneath the endocardium and a similar one beneath the epicardium, but the muscle between was little involved. There were areas of damage throughout the muscle of all four chambers of one heart, whereas in others there were small, localized patches of necrosis, in addition to the more extensive subendocardial damage. The damaged muscle fibers were usually palely staining and retained their striations, although the transverse ones were frequently difficult to see. Cross fragmentation, sometimes with fibrosis between the opposing ends, was common, and in these cases the process appeared to represent a "melting," for the distribution of sarcoplasm was uniform to the point of fracture. In some sections the muscle fibers were granular, and in others there was a loss of sarcoplasm, producing a moth-eaten appearance. This even involved the media of the arterioles in three cases, so that the architecture of the wall was destroyed but the lumen was not encroached upon. In only one case was the lumen of a small coronary artery obstructed, and this probably was the result rather than the cause of the degenerative process in the muscle, for the latter extended far beyond the distribution of this particular vessel.

These pathologic changes were interpreted as primarily degenerative in character, rather than inflammatory, because the usual cellular infiltration of inflammation was not predominant. The terms "interstitial," "isolated," "diffuse," and "primary" myocarditis have been used⁴⁻⁶ to describe the lesions (cellular infiltration) encountered in the hearts of patients who died from heart failure without obvious cause.

Although the changes observed in our cases do not justify the diagnosis of myocarditis, there was considerable similarity between the clinical course of our patients and that described for those with myocarditis. Others⁷ have reported "nonsuppurative myocardial degeneration with dilatation and hypertrophy" in children, and "idiopathic myocardial degeneration"⁸ in the puerperal period, with descriptions of myocardial damage which more closely approximates the observations in our cases. These authors were unable to suggest a satisfactory explanation for the pathologic changes, but, unlike their patients, four of ours gave a history or had serologic evidence of syphilis, with suggestive changes in the aorta which did not affect the coronary ostia or aortic valve enough to account for the myocardial damage. The fifth patient was a negro who gave no history of infection, treatment, or a positive serologic reaction. Although the spinal fluid was not examined, the aorta was not grossly involved and, therefore, no definite evidence of syphilis was found in this case. The possibility that syphilis was responsible for the cardiac manifestations in these cases cannot be dismissed, however, even though the ability of the *Treponema pallidum* to attack the myocardium directly, except in the production of gummatous lesions, has never been decisively proved. In the earlier stages of syphilitic cardiovascular disease, manifested only by aortitis, it is not uncommon for the patient to complain of symptoms suggesting myocardial insufficiency, frequently without pain referred to the heart. This is difficult to explain as a result of aortic involvement alone, even if some degree of coronary ostia occlusion is assumed, and modern textbooks⁹⁻¹⁰ admit the possibility that syphilitic myocarditis may occur, but consider it a rare phenomenon. Certainly the clinical criteria for the diagnosis are vague, and the final conclusion in such cases has been reached partly by exclusion of other causes. Hamman and Rich¹¹ and Magill¹² reported what they considered to be cases of syphilitic myocarditis, characterized by a history or serologic evidence of syphilis, cardiac enlargement, and myocardial insufficiency, without any of the usual causes associated with these manifestations. Their diagnoses depended to some extent upon histologic evidence, although they were not able to demonstrate spirochetes in the tissue or isolate them by the injection of macerated muscle into a rabbit's testicle. The pathologic criteria are uncertain, however, for there is little agreement as to the microscopic appearance of nongummatous syphilitic myocardial involvement.¹³⁻¹⁷ Warthin's^{18, 19} demonstration of spirochetes in the myocardium in many cases of syphilis has never been successfully repeated, and the other diagnostic criteria, such as interstitial edema, focal accumulations of round cells, and fibrosis, have been observed by us, as well as by others,¹⁴ in cases of myocardial insufficiency when syphilis played no part. Therefore, the fact that the pathologic process in our cases seemed to us to be more degenerative

than inflammatory would not necessarily exclude syphilis as the causative factor. No other etiology was suggested by long clinical observation and pathologic study, although it should be emphasized that the syndrome and even the pathologic changes might easily have been ascribed to coronary arteriosclerosis, employing the usual criteria, if it had not been known that the coronary arteries were not obstructed in any way.

The five cases reported here represent only a small percentage of all patients with cardiac disease, but it is our impression that this group might be easily enlarged by the inclusion of other patients, particularly negroes with syphilis who present evidence of cardiac enlargement and myocardial damage and insufficiency, without apparent adequate cause. The proof that syphilis is of etiologic importance in these instances, however, awaits the development of more exact criteria.

SUMMARY

Five cases of fatal heart failure, with necropsy, are reported.

All of the patients showed cardiac hypertrophy and myocardial degeneration, without evidence of hypertension, valvular disease, coronary artery disease, or any of the less common causes of these structural changes.

Four of the five patients presented suggestive evidence of syphilis in the history, serologic reaction, or aorta, and the possible etiologic relationship of this disease to the myocardial lesions is discussed.

REFERENCES

1. Bell, E. T., and Clawson, B. J.: Primary (Essential) Hypertension, *Arch. Path.* 5: 939, 1928.
2. Kaplan, B. I., Clark, E., and de la Chapelle, C. E.: A Study of Myocardial Hypertrophy of Uncertain Etiology, Associated With Congestive Heart Failure, *AM. HEART J.* 15: 582, 1938.
3. Levy, R. L., and Rousselot, L. M.: Cardiac Hypertrophy of Unknown Etiology in Young Adults. A Clinical and Pathological Study, *AM. HEART J.* 9: 178, 1933.
4. Scott, R. W., and Saphir, O.: Acute Isolated Myocarditis, *AM. HEART J.* 5: 129, 1929.
5. De la Chapelle, C. E., and Graef, I.: Acute Isolated Myocarditis, *Arch. Int. Med.* 47: 942, 1931.
6. Hansmann, G. H., and Shenken, J. R.: Acute Isolated Myocarditis, *AM. HEART J.* 15: 749, 1938.
7. Kugel, M. A., and Stoloff, E. G.: Dilatation and Hypertrophy of the Heart in Infant and Young Children With Myocardial Degeneration and Fibrosis (So-Called Congenital Idiopathic Hypertrophy) *Am. J. Dis. Child.* 45: 828, 1933.
8. Gouley, B. A., McMillan, T. M., and Bellet, S.: Idiopathic Myocardial Degeneration Associated With Pregnancy and Especially the Puerperium, *Am. J. M. Sc.* 194: 185, 1937.
9. White, Paul D.: *Heart Disease*, ed. 2, New York, 1937, Macmillan Co., p. 274.
10. Levine, Samuel A.: *Clinical Heart Disease*, Philadelphia, 1936, W. B. Saunders Co., p. 181.
11. Hamman, L., and Rich, A. R.: A Case of Syphilitic Myocarditis, *Internat. Clin.* 4: 221, 1934.
12. Magill, T. P.: Syphilitic Myocarditis, *Bull. Johns Hopkins Hosp.* 57: 22, 1935.
13. Boyd, W.: Acute Myocardial Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* 14: 35, 1930.

14. Saphir, Otto: Syphilitic Myocarditis, Arch. Path. 13: 226, 436, 1932.
15. Brooks, H.: The Heart in Syphilis, Am. J. M. Sc. 146: 513, 1913.
16. Brooks, H., and Carroll, J. H.: The Symptoms and Diagnosis of Involvement of the Heart in Syphilis, New York State J. Med. 13: 328, 1913.
17. Norris, J. C.: Syphilis of the Myocardium and Coronary Arteries, J. A. M. A. 108: 169, 1937.
18. Warthin, A. S.: The Persistence of Active Lesions and Spirochetes in Tissues of Clinically Inactive or "Cured" Syphilis, Am. J. M. Sc. 152: 508, 1916.
19. Warthin, A. S.: Primary Tissue Lesion in the Heart Produced by Spirocheta Pallida, Am. J. M. Sc. 147: 667, 1914.

A SYNDROME DUE TO OCCLUSION OF ALL ARTERIES ARISING FROM THE AORTIC ARCH

REPORT OF A CASE FEATURED BY PRIMARY THROMBOCYTOSIS AND AUTOHEMAGGLUTINATION

P. M. AGGELER, M.D., S. P. LUCIA, M.D., AND J. H. THOMPSON, M.D.
SAN FRANCISCO, CALIF.

COMPLETE absence of pulsations in all arteries of the upper extremities and neck is extremely unusual. We take this opportunity to report such a case, in which bilateral cataracts, proliferative retinitis, and atrophic rhinitis were complications. Other unusual abnormalities were thrombocytosis and autohemagglutination.

CASE REPORT

U. C. H. No. U61721 was a Spanish woman, aged 29 years.

First Entry.—July 30, 1940, to Sept. 14, 1940.

Present Illness.—Four years before entry the patient suddenly collapsed and fell to the floor; following this she became progressively weakened. Her hands and feet felt cold and at times were blue. She suffered from palpitation and a transient substernal ache brought on by slight exertion. She became dizzy on arising quickly from the supine position. Her memory was markedly impaired for both recent and remote events, and she suffered from emotional instability. Her vision became blurred because of gradually developing cataracts. In December, 1938, a cataract was removed from the right eye without restoration of vision, and from November, 1939, she had been totally blind.

The past history and family history were noncontributory. The patient had never used tobacco or alcohol and had not taken dinitrophenol. There was no history of syphilis. Four children were living and well, aged 9 years, 7 years, 5 years, and 2 months, respectively. One miscarriage (twins) occurred shortly before the onset of the present illness.

Additional history obtained from physicians who had previously attended the patient revealed that between February and June, 1931, a number of blood pressure readings in the arms varied between 120/70 and 136/80. In July, 1937, the blood pressure in the arms was 100/60. In November, 1938, no blood pressure measurements could be obtained in either arm, and the radial pulses were not palpable. The blood pressure in the legs was 160 to 170, systolic, with indefinite diastolic readings. Oscillometric readings were zero in both arms, 6 in the left thigh, and 4 in the right thigh. A strong pulsation was present in the suprasternal notch. The carotid pulse was palpated on the right, but not on the left. A loud to-and-fro murmur, transmitted into the neck, was heard over the left sterno-clavicular region, left supraclavicular area, and left second intercostal space. Roentgenograms of the chest showed nothing abnormal except rudimentary seventh cervical ribs. A scalenectomy and resection of the left cervical rib, which were done January 13,

From the Department of Medicine, University of California Medical School.
Received for publication May 23, 1941.

1939, revealed a fibrosed subclavian vein crossing the first rib, medial to the scalenus anticus tendon; the subclavian artery was not seen. In December, 1938, examination of the ocular fundi revealed a meshwork of new blood vessels growing over both discs. The temporal half of the right lens was opaque, and the patient was not able to count fingers with this eye at a distance of more than 1 foot. Vision in the left eye was 20/40. A cataract was removed from the right eye without restoration of vision. Laboratory examination at that time revealed that the basal metabolic rate was -12 per cent, the serum calcium, 9.5 mg. per cent, the serum phosphorus, 3.35 mg. per cent, the urea clearance, 62 per cent, the venous pressure (antecubital vein), 10 cm. of water, and that the arm-to-tongue and arm-to-lung circulation times were 16.5 and 8.5 sec., respectively.

Physical Examination.—The patient was a well-developed, poorly nourished woman. The skin was warm and dry. The lymph nodes were not enlarged. The extraocular movements were normal. The pupils were dilated and irregular, and did not react to light or in accommodation. The bulbar conjunctivae were markedly injected. Slit-lamp examination of the conjunctivae showed clumps of erythrocytes traveling as units in the larger vessels; the normal differential ratio of flow of blood constituents (from center to periphery of vessel) was not present; the small venules and capillaries contained columns of blood cells in rouleaux. Ophthalmoscopic examination (right eye): linear incisional scar of the cornea; optic nerve head atrophic, margins blurred, irregular, and without perceptible elevation or depression; many arterioles occluded and obliterated and some bloodless (ghost-vessels); large areas of retinal hemorrhage; macula not seen. A dense cataract prevented seeing the left fundus. Light and color perception was intact, but light projection was questionable in all but the nasal field of the left eye. There was faint perception of light in the right eye. The nasal mucous membrane was crusted, and there was a large perforation of the septum. Marked periodontoclasia was present. The tonsils were atrophic. The thyroid was not enlarged. There was marked pulsation of the vessels in the suprasternal notch. The chest, breasts, and lungs were normal. The left half of the diaphragm was elevated 6 cm. above the right. The area of cardiac dullness extended 6 cm. to the left of the midsternal line in the fifth intercostal space; the heart sounds were loud and snapping; the rhythm was normal and the rate was 102 per minute; a soft, blowing, systolic murmur was heard at the apex, and another was localized over the aortic area; there were no thrills; the aortic second sound was louder than the pulmonic second. The abdomen, extremities, and nervous system were normal. Psychiatric examination disclosed impaired memory for recent and past events. Examination of the peripheral vascular system showed no unusual color or thermal changes. The carotid, subclavian, brachial, radial, ulnar, and intercostal arteries were not palpable or pulsatile. The pulsations in the abdominal aorta and arteries of the lower extremities were normal. No collateral circulation was visible over the chest or shoulder girdle. The blood pressure was not obtainable in the arms; in the left leg it was 160/100; in the right leg, 140/100.¹ The oscillometric readings were zero in both arms, 4 in the right lower leg, and 3.5 in the left lower leg. The venous pressure was not increased. There were very few visible or palpable superficial veins. Tests for reactive hyperemia in both arms were normal. There was neither excessive blanching on elevation of the limbs nor cyanosis in the dependent position.

Laboratory Data.—Hemoglobin was 9.6 Gm., or 70 per cent; erythrocyte count, 4,400,000; leucocyte count, 8,900; P.M.N., 42 per cent (filaments 40 per cent, non-filaments 2 per cent); lymphocytes, 40 per cent; monocytes, 18 per cent.

Platelet count (Rees and Ecker): 10 platelet counts during the six weeks' observation varied between 1,200,000 and 1,500,000.

Packed cell volume was 35.

Sedimentation rate (Linzenmeier) was 14 minutes.

Auto-agglutination of erythrocytes occurred at body, room, and icebox temperature.

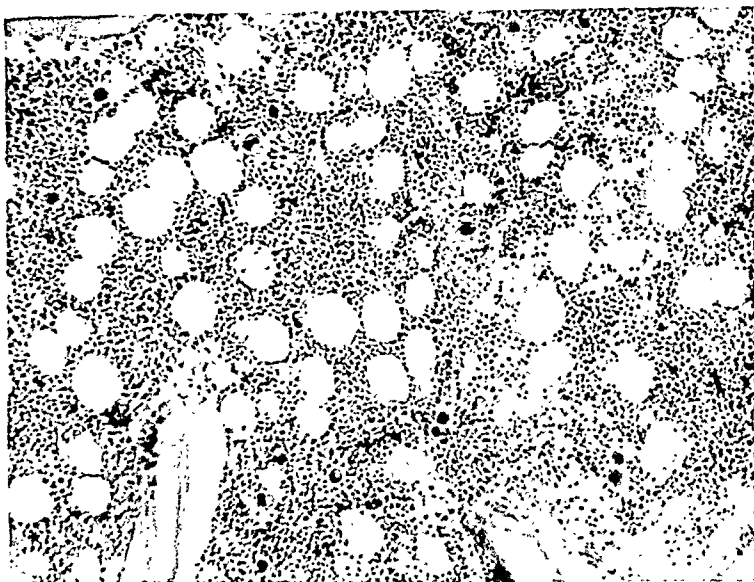


Fig. 1.—Sternal bone marrow biopsy, demonstrating increased numbers of megakaryocytes ($\times 120$, hematoxylin and eosin stain).

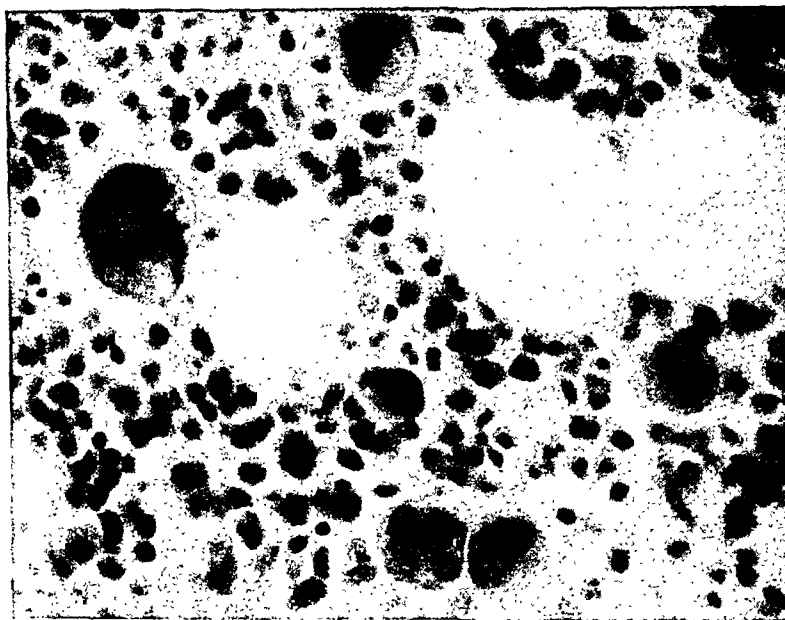


Fig. 2.—High power magnification ($\times 700$) of sternal bone marrow biopsy, demonstrating megakaryocytes and active erythropoiesis (hematoxylin and eosin stain).

Sternal biopsy (Figs. 1 and 2): Hyperplasia of both myeloid and erythropoietic series was observed. Megakaryocytes were normal in appearance, but increased in number (one to five per oil-immersion field). Eosinophiles were present in great numbers. There was an excessive number of platelets on the smear of the material obtained by sternal puncture. Intact megakaryocytes were infrequent, but many large agminations of nuclear material, surrounded by masses of adherent thrombocytes, were present. These tended to form "streamers" during the course of making smear preparations (Figs. 3, 4, and 5).

Capillary fragility (Daldorf) was slightly increased.
Plasma ascorbic acid was 0.19 mg. per cent.
Bleeding time (Ivy) was 3 minutes.
Coagulation time (Lee and White) was 8 minutes.
Recalcified plasma coagulation time² was 90 seconds.

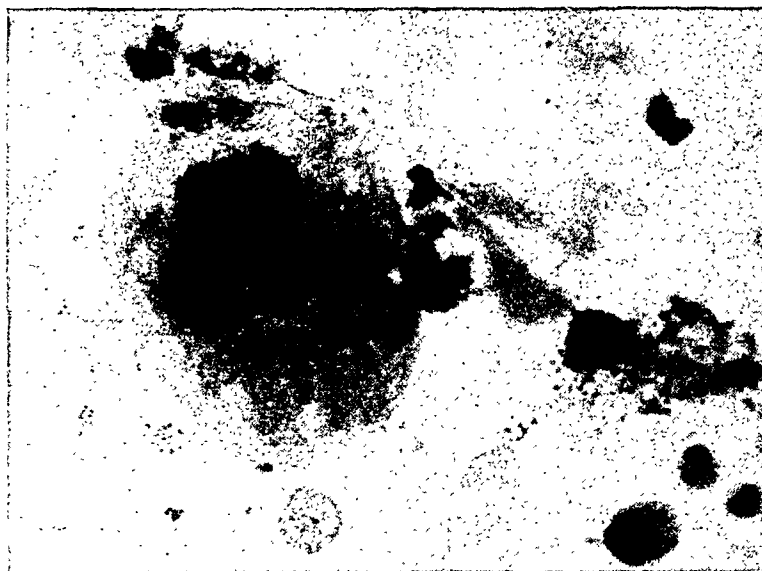


Fig. 3.—Smear preparation demonstrating megakaryocyte obtained by sternal bone marrow puncture ($\times 700$, Giemsa stain).

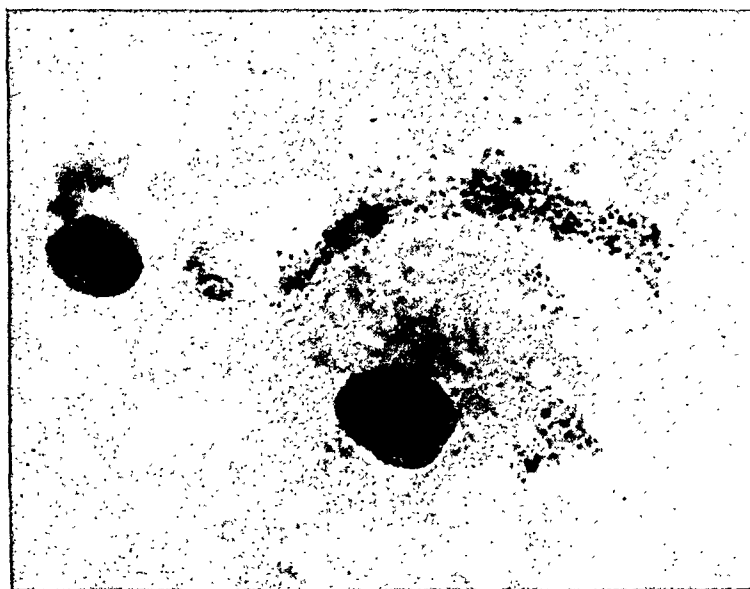


Fig. 4.—Smear preparation demonstrating megakaryocyte obtained by sternal bone marrow puncture ($\times 700$, Giemsa stain).

Prothrombin concentration (Quick) was 110 per cent.
Clot retraction was normal.
Urinalysis, P.S.P. excretion, Mosenthal, Diodrast clearance tests,* and intravenous pyelograms were normal.
Stool was normal.
Serum calcium was 10.85 mg. per cent.

*The authors are indebted to Dr. Meyer Friedman for this determination.

Serum phosphorus was 5.20 mg. per cent.

Serum proteins: Total, 8.00 per cent; albumin, 4.21 per cent; globulin, 3.79 per cent.

Circulation time (Decholin) was 15.5 sec.

Kolmer and Kahn tests were negative.

Electrocardiogram showed sinoauricular tachycardia. Rate was 106. T_1 was diphasic; T_2 , inverted; T_4 , notched and low.

Skin temperatures over the entire body were essentially normal.



Fig. 5.—Smear preparation demonstrating agminations of platelets obtained by sternal puncture ($\times 700$, Giemsa stain).

Biopsy.—Histologic examination of sections of an artery 2 mm. in diameter, situated in the usual location of the right brachial artery, and of sections from the right pectoral, biceps, and gastrocnemius muscles revealed normal striated muscle and normal appearing, thin-walled arterioles and venules.

Roentgenologic Examinations: *Chest* (including fluoroscopy).—A cervical rib was present on the right side. There was a small fragment of bone in the region from which the left cervical rib had been removed. There were no abnormal aortic pulsations. The heart and great vessel shadows were within normal limits. The left half of the diaphragm was elevated and moved physiologically, but with a lag. *Abdomen.*—The spleen appeared to be of normal size. *Skeletal system.*—The bony density was essentially normal. There was a slight alteration of the trabecular pattern of the ileum and of the inferior articular process of the second lumbar vertebra. There were a few minor cystic changes in the greater tuberosity of the right humerus and in the neck of the left femur. The vascular markings of the skull were prominent symmetrically. The joint surfaces and joint spaces were normal.

Second Entry.—Feb. 26, 1941, to March 8, 1941.

During the intervening six months the patient had noted increasing weakness, frequent headaches, and occasional nervous spells. Her nose had become tender, and two weeks before entry the bridge had collapsed, producing a saddle deformity. All of her upper teeth had been removed. Her general condition was essentially as before, except that she appeared to be more weakened. There was marked crusting of the mucous membrane in both nares. There was a mature cataract in the left eye. The right eye showed an old retinitis proliferans, with new-formed

vessels and partial detachment of the retina. The presence of hemorrhages signified that the process was still active. Examination of the heart was of interest in that the murmurs which had been previously heard were now inaudible. There was a marked increase in the amount of hair on the legs.

Diodrast cardiograms, done according to the Robb-Steinberg technique, revealed no abnormalities of the heart or aorta. Spinal fluid examination showed that Kolmer was negative; colloidal gold, 0012210000; protein, 43.1 mg. per cent; cell count, 3 lymphocytes. Infrared photographs revealed no increase in venous circulation. Two platelet counts were 820,000 and 890,000, respectively.

REVIEW OF PREVIOUS CASES

Five cases of complete absence of pulsations in the carotid arteries and in the arteries of both upper extremities have been reported; in all of them the loss of pulsation was presumably due to syphilitic involvement of the transverse arch of the aorta (Table I). There are striking similarities in the symptomatology in these cases and the case herein reported. In all cases, the pulsations in the vessels of the lower extremities were normal. There were evidences of circulatory insufficiency in the arms in only one case.⁷ The central nervous system symptoms included headaches, vertigo, syncope, emotional instability, delirium, loss of memory, aphasia, and hemiplegia. Vertigo and syncope were frequently brought on by arising quickly from the supine position. Ocular manifestations included photophobia, choroiditis, cataracts, and proliferative retinitis. The subject of this report had, in addition, atrophic rhinitis. It seems probable that the essential pathologic process was similar in all of the cases reviewed, i.e., occlusion of the large vessels arising from the arch of the aorta.

Eden⁸ has recently reviewed the literature dealing with the vascular complications arising from cervical and abnormal first thoracic ribs. Those patients who had absence of the radial pulse showed evidences of circulatory insufficiency in the affected arm. In a few, the pulsations returned after removal of the cervical rib. In no instance were both radial pulses absent, and never were abnormalities of the carotid pulse observed. Although cervical ribs were present bilaterally in our case, they did not appear to be the cause of the vascular abnormalities.

Absence of pulsation in the carotid arteries and in the arteries of the arms has occasionally been noted in cases of dissecting aneurysm of the aorta.⁹ However, such a diagnosis was considered untenable in this case because there was no history of chest pain, dyspnea, or hypertension, and there were no evidences of circulatory insufficiency in the arms.

Nygaard and Brown¹⁰ have described "essential thrombophilia" as a condition occurring in previously healthy subjects, characterized by sudden, widespread occlusion of major arteries and veins, with marked signs of circulatory insufficiency often resulting in gangrene, and with insignificant histopathologic changes in the involved vessels. They observed variations in the plasma coagulation time in some of their pa-

tients. In the one case in which the platelet count was significantly elevated, no histopathologic examination of the tissues was performed, so that it cannot be classified as a proved case of "essential thrombophilia." It is apparent that our patient's disease did not resemble this condition. The constant thrombocytosis and the absence of any demonstrable cause of the vascular occlusions suggested the possibility that our patient was suffering from an obscure thrombotic process due to accelerated and pathologic coagulation of the blood. An increase in the number of platelets in the circulating blood, occurring as a primary disease,¹¹⁻¹³ is an extremely rare condition, although secondary thrombocytosis is not uncommon in myeloid leucemia, polycythemia, megakaryocytic leucemia, and after splenectomy.¹⁴ Among the reported cases of primary thrombocytosis, in that of Epstein, et al.,^{11, 15} there was atrophy of the spleen, and, in that of Uotila,¹² marked leucocytosis and, at times, polycythemia. In one of the two cases reported by Rowlands and Vaizey,¹³ the spleen was enlarged to the level of the umbilicus and slight polycythemia was present. In the subject of our report, no condition known to be associated with a secondary elevation of the platelet count was found to be present. There was a moderate increase in the megakaryocytes of the sternal bone marrow, and in the smear of the material obtained by sternal puncture there were a few intact megakaryocytes and many large agminations of nuclear material surrounded by masses of adherent thrombocytes. The spleen was not palpable, and roentgenologically it was found to be of normal size. Aside from the increased platelet count, no abnormalities in the bleeding and clotting mechanism of this patient were demonstrated.

A further investigation of the coagulative potency of the plasma was performed in the following manner. Nine cubic centimeters of blood were withdrawn from the antecubital vein, mixed quickly with 1 c.c. of a 1.34 per cent solution of sodium oxalate in a test tube, and centrifugalized at 2,000 r.p.m. for 10 minutes. Varying amounts of the supernatant plasma were pipetted into 13 by 100 mm. glass tubes, and placed in a water bath at 37° C. Two cubic centimeters of blood obtained from the antecubital vein of a patient with hemophilia (whole blood coagulation time, 50 minutes) were added to each of these tubes and the coagulation time measured to the nearest half minute. The results are given in Table II. It can be seen readily that there was no significant difference in the ability of this plasma and normal plasma to accelerate the coagulation of hemophilic blood.

Among the many factors which favor the agglutination of platelets, and hence influence the occurrence of thrombosis, is to be included an increase in the concentration of the weakly electronegative proteins, i.e., fibrinogen and globulin. Autohemagglutination, associated with hyperglobulinemia, is often found in patients with multiple myeloma.

TABLE I

PREVIOUSLY REPORTED CASES OF COMPLETE ABSENCE OF PULSATION OF ARTERIES
ARISING FROM AORTIC ARCH

AUTHOR	AGE	SEX	SYMPTOMS	SIGNS	PATHOLOGIC CHANGES
Shikhare ³	Middle aged	M	Vertigo, photophobia, and periods of syncope	All arteries of upper half of body non-pulsatile	Autopsy: Fusiform aneurysm of ascending and transverse aorta. Lumina of large vessels arising from arch occluded by ante-mortem thrombus, which had propagated from large clot in aortic arch
Crawford ⁴	52	M	Occipital headaches, pain in back of neck, dyspnea, vertigo, cough, and tingling of left thumb. Radial pulse noted to have been absent 6 weeks previously	Radial, brachial, and external carotid pulsations absent. Systolic blood pressure in legs, 125 mm. Hg	Fluoroscopy: Aneurysm of arch and descending aorta
Kampmeier and Neumann ⁵	35	M	Recurrent periods of vertigo and syncope, particularly on arising from supine position. Left radial pulse noted to have been absent 2 years previously	Radial, brachial, and carotid pulsations absent. Visible and palpable systolic pulsations at angle of left scapula. B.P. in legs, 178/110	Fluoroscopy: Aneurysm of ascending and transverse aorta
Cohen and Davies ⁶	60	M	Onset of symptoms 12 years previously, accompanied by cataract of left eye. Headache, attacks of syncope, delirium, and cardiac failure	Radial and carotid pulsations absent. Numerous small pulsating subcutaneous vessels over chest and upper abdomen. Systolic blood pressure in arms, 40 to 50 mm. Hg, in legs, 210 mm. Hg. Marked retinal arteriosclerosis of right eye. Left eye obscured by cataract	Autopsy: Fusiform aneurysm of ascending and transverse aorta. Orifices of all vessels arising from arch obliterated

TABLE I—CONT'D

AUTHOR	AGE	SEX	SYMPTOMS	SIGNS	PATHOLOGIC CHANGES
Maurer ⁷	33	F	Right hemiplegia 3.5 years previously, followed by complete aphasia and numerous periods of syncope, and weakness brought on particularly by sitting upright and relieved by lying down	Skin over shoulder girdle, upper extremities, head, and neck less warm than rest of body. Lips and nail beds cyanotic. No pulsations in carotids or arteries of upper extremity. Arms and hands atrophic. Systolic B.P. in legs, 120 mm. Hg	Autopsy: Sacular aneurysm of transverse arch of aorta. Arch filled with laminated clot with thrombotic extensions completely occluding innominate, left common carotid, and left subclavian artery

TABLE II

AMOUNT OF HEMOPHILIC BLOOD (C.C.)	AMOUNT OF PLASMA (C.C.)	COAGULATION TIME	
		WITH PATIENT'S PLASMA (MIN.)	WITH NORMAL CONTROL PLASMA (MIN.)
2	0.01	26	24
2	0.05	10	8
2	0.10	5.5	5.5

However, thrombosis is an unusual occurrence in this disease. Wintrobe and Buell¹⁶ found two such reports in the literature, and added a third. Their patient had thrombosis of the retinal veins and symptoms suggesting Raynaud's disease. McCombs and McElroy¹⁷ reported an instance of autohemagglutination due to a cold-agglutinin in a patient with peripheral vascular symptoms. In our case, the globulin content of the serum was only slightly increased. Marked agmination of the erythrocytes was observed in the small blood vessels in the conjunctiva. Autohemagglutination due to a pseudo-agglutinin was observed in vitro. Roentgenologic examination of the entire skeleton revealed no evidence of myeloma. The plasma cells were not increased in the sternal bone marrow.

Because of the localization of the occlusive process to the large vessels arising from the arch of the aorta, it seems unlikely that changes in the blood plasma or an increase in the number of circulating blood platelets could have been entirely responsible for this condition. The etiology in our patient therefore remains obscure.

SUMMARY

A syndrome due to occlusion of all of the vessels arising from the arch of the aorta has been described, and a case reported. The condition is characterized by complete absence of pulsations in the carotid arteries

and in the arteries of both upper extremities. The following may be present: (1) central nervous system symptoms, including headaches, vertigo, syncope, emotional instability, delirium, loss of memory, aphasia, and hemiplegia; (2) ocular manifestations, including photophobia, choroiditis, cataracts, and proliferative retinitis; (3) atrophic rhinitis; and (4) atrophy of the arms and hands.

Although syphilis was presumed to be the etiologic agent in the previously reported cases, no evidence of its presence could be found in this case. The exact etiology is unknown, although thrombocytosis and auto-hemagglutination may have been contributing factors.

REFERENCES

1. Standardization of Blood Pressure Readings, *AM. HEART J.* 18: 45, 1939.
2. Aggeler, P. M., and Lucia, S. P.: The Potency of Blood Coagulating Substances, *Am. J. M. Sc.* 199: 181, 1940.
3. Shikhare, P. V.: Notes on a Remarkable Case of Absence of Pulsation in the Arteries of the Upper Parts of the Body, *Indian J. Med.* 2: 326, 1921.
4. Crawford, J. R.: Bilateral Pulse Obliteration in Thoracic Aneurysm, *J. A. M. A.* 65: 1395, 1921.
5. Kampmeier, R. H., and Neumann, V. F.: Bilateral Absence of Pulse in the Arms and Neck in Aortic Aneurysm, *Arch. Int. Med.* 45: 513, 1930.
6. Cohen, H., and Davie, T. B.: Bilateral Obliteration of the Radial and Carotid Pulses in Aortic Aneurysm, *Lancet* 1: 582, 1933.
7. Maurer, E.: Absence of Pulse in the Vessels of the Upper Extremities and Neck in Aneurysms of the Aortic Arch, *AM. HEART J.* 17: 716, 1939.
8. Eden, K. C.: The Vascular Complications of the Cervical Ribs and First Thoracic Rib Abnormalities, *Brit. J. Surg.* 27: 111, 1939.
9. Shennan, T. N.: Dissecting Aneurysms, Medical Research Council Special Report Series No. 193, 1934.
10. Nygaard, K. K., and Brown, G. E.: Essential Thrombophilia, *Arch. Int. Med.* 59: 82, 1937.
11. Epstein, E., and Kretz, J.: Über einen Fall von hochgradiger Thrombocytenvermehrung, *Klin. Wchnschr.* 9: 1177, 1930.
12. Uotila, U.: On Hemorrhagic Thrombocythemia, *Acta med. Scandinav.* 95: 136, 1938.
13. Rowlands, R. A., and Vaizey, J. M.: Primary Thrombocythaemia, *Lancet* 2: 1217, 1938.
14. Tocantins, L. M.: The Mammalian Blood Platelets in Health and Disease, *Medicine* 17: 2, 155, 1938.
15. Epstein, E., and Goedel, A.: Hämorrhagische Thrombocythämie bei vasculärer Schrumpfmilz, *Virchows Arch. f. path. Anat.* 292: 233, 1934.
16. Wintrobe, M. M., and Buell, M. V.: Hyperproteinemia Associated With Multiple Myeloma, *Bull. Johns Hopkins Hosp.* 52: 156, 1933.
17. McCombs, R. P., and McElroy, J. S.: Reversible Autohemagglutination With Peripheral Vascular Symptoms, *Arch. Int. Med.* 59: 107, 1937.

Department of Clinical Reports

PASSAGE OF A HOLLOW NEEDLE INTO THE VENOUS BLOOD STREAM TO THE HEART, THROUGH THE CARDIAC WALL, AND INTO THE THORAX

REPORT OF A CASE

SHEPARD SHAPIRO, M.D.

NEW YORK, N. Y.

THIS report is one of a case in which a needle which was being used for an intravenous injection became separated from the hub and entered the blood stream.

The circumstances were as follows: A physician was giving an injection into the left cephalic vein of a 45-year-old white man on May 28, 1938. Upon completion of the injection he applied pressure at the point of puncture with a small pledget of cotton, in order to avoid leakage, and attempted to withdraw the needle. Only the hub of the needle, however, remained attached to the syringe. Diligent search of the surrounding tissue failed to locate the lost part of the needle. The patient did not complain of pain or other symptoms. Roentgenograms of the arm and chest, taken the same day, failed to show the needle. However, the patient was observed at frequent intervals thereafter, and, on June 24, 1938, about one month after the injection, a posteroanterior roentgenogram of the chest revealed a linear shadow, the dimensions of which corresponded exactly to those of the lost needle. The needle was lying horizontally at the level of the eighth thoracic vertebra (Fig. 1). Fluoroscopic examination showed that the needle lay outside the heart, and appeared to be embedded in the prepericardial fat between the inferior surface of the apex of the heart and the left dome of the diaphragm.

The patient has not had any complaint referable to the circulation, heart, lungs, or pleura. Roentgenographic and fluoroscopic examination of the chest on July 7, 1938, showed that the shadow was in the same location. Four subsequent examinations, the last on March 27, 1940, revealed no alteration in the position of the needle.

The electrocardiograms were normal. The blood pressure has been constantly 120/80. The heart rate has averaged 76 per minute, and the

Received for publication Oct. 5, 1940.

rhythm has been normal. Cardiac murmurs have never been heard, and the size of the heart has remained normal. At present the patient is active and works as a commercial artist, which is his usual occupation.

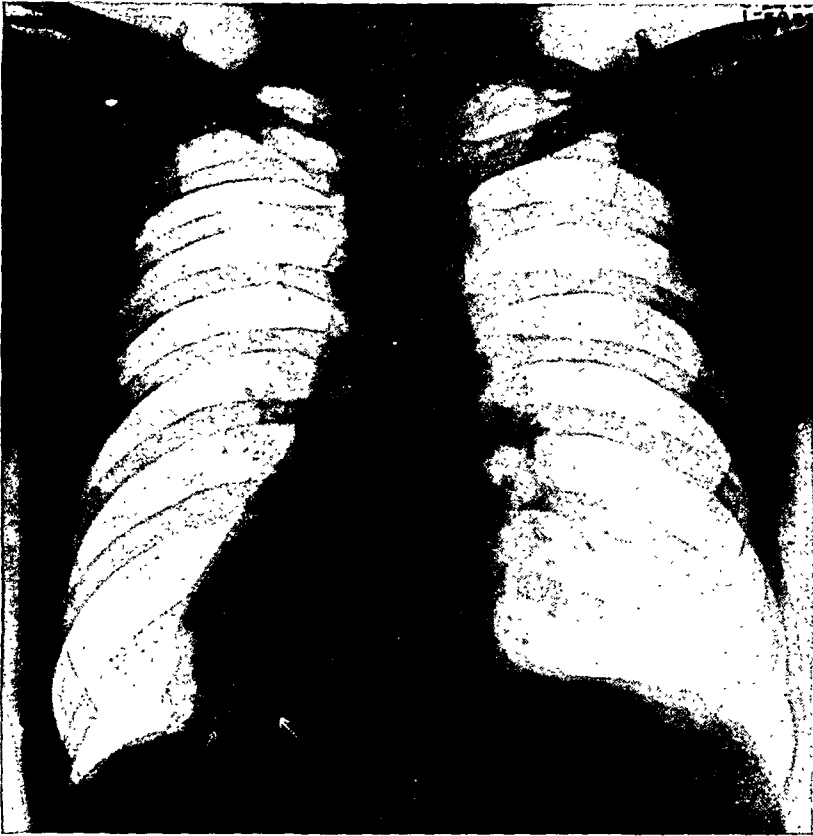


Fig. 1.—The arrows point to the needle shadow between the inferior surface of the heart and the left dome of the diaphragm.

DISCUSSION

From its location in the chest, it is apparent that the needle must have entered the heart, passed through its wall, and lodged in the silent area where it now rests. The course of the needle after it entered the venous blood stream must have been through the left cephalic vein, axillary vein, subclavian vein (up to this point all of the veins possess valves), innominate vein, superior vena cava, and, finally, the right side of the heart.

There are three pathways by which foreign bodies may enter the heart. The first, and most common, is directly through the chest wall, as in the case of gunshot wounds or the thrust of a sharp instrument. Examples of these abound in the literature.¹⁻⁴

The second pathway is through tissue from a distant part of the body; the foreign body is forced by muscular contraction along a more or less circuitous route, possibly by following paths of least resistance, until by chance it eventually reaches the thorax and the heart. It is probable that only a sharp instrument, such as a nail or needle, can

perform this feat. A striking example of this was reported by Rea and Hoover;⁵ a needle entered the foot of a patient when he accidentally stepped upon it, and four years later he died as the result of thoracic disease induced by the passage of the needle through the pleura and pericardium. At autopsy the needle was found lodged in the heart.

The third pathway is illustrated by the case reported in this paper. Another remarkable instance of the same route was reported by Blaha.⁶ In his case a soft rubber catheter was introduced into a gravid uterus to induce an abortion, and, when the uterus expelled its contents, the catheter was not among them. The patient became infected and died. At autopsy the catheter, 24 cm. long and 4 mm. in diameter, was found lying in a channel formed by the inferior vena cava, the right auricle, the superior vena cava, the left innominate vein, and the internal jugular vein. This case and the one described in this paper illustrate how relatively large bodies may gain entrance into the venous blood stream and be carried to the heart.

The importance of investigating the flexibility and sturdiness of each needle before use, especially for intravenous injections, is emphasized by the present report. It should be realized that the needle consists of two parts, namely, a flexible cannula and a rigid hub, and that the junction of these two parts is the weak spot in the construction of every needle. It is consequently important (when administering any injection) not to introduce the needle more than three-fourths of its length, so that, if it should accidentally become separated from the hub, it might still be possible to grasp its free end before it becomes completely submerged in the tissues.

SUMMARY

1. A case is reported in which a hollow needle entered the venous blood stream, was carried to the heart, penetrated its wall, and came eventually to lie in the prepericardial fat between the heart and the diaphragm, without producing any untoward symptoms.

2. The pathways by which foreign bodies may enter the heart are described.

3. The hazard described in this paper, although a rare one, warrants the recommendation that the flexibility and sturdiness of needles be carefully tested before they are put to intravenous use.

The author is grateful to Dr. A. S. Hartstein and Dr. B. Kurz, of New York City, for permitting him to examine their records of this case.

REFERENCES

1. Bland-Sutton, Sir John: A Lecture on Missiles as Emboli, *Lancet* 1: 773, 1919.
2. Cope, Z.: Extraction of Sewing Needle From the Heart, *Lancet* 1: 813, 1920.

3. Goldberger, H. A., and Clark, H. E.: Migration of Needle into Heart Through Chest Wall: Surgical Removal, Electrocardiographic and Roentgenographic Studies, J. A. M. A. 105: 193, 1935.
4. Fair, George L.: Foreign Body in the Heart: Report of a Case With Retention of a Large Needle With Recovery, New York State J. Med. 35: 453, 1935.
5. Rea, Charles, and Hoover, P. A.: An Unusual Case of a Needle Found in the Heart at Necropsy, J. A. M. A. 109: 266, 1937.
6. Blaha, J.: Embolische Verschleppung eines Fremdkörpers (Gummikatheter) ins Herz bei einem kriminellen Abortus, Zentralbl. f. Gynäk. 59: 746, 1935.

45 EAST 85 ST.

Department of Reviews and Abstracts

Selected Abstracts

Eyster, J. A. E., and Meek, W. J.: The Sequence of Fractionate Contraction at Different Surface Regions on the Right Auricle and Ventricles of the Dog's Heart. *Am. J. Physiol.* 134: 513, 1941.

The sequence of occurrence of fractionate contraction at the different surface regions of the right auricle and ventricles of the dog's heart is determined by recording differential potential-time curves from the various regions along with a constant reference curve. The results are indicated in the accompanying figure.

The fact that no criterion is available at present which can be used to determine the instant of "excitation" of a region of heart muscle, is brought out and discussed.

AUTHORS.

Frey, J.: Experimental Observations on the Effects of Hydrostatic Forces on the Circulation. *Arch. f. Kreislaufforsch.* 7: 329, 1940.

This is an extensive investigation on the effect of posture upon the circulation in animals, healthy subjects and cardiac patients with and without congestive heart failure. Among the principal conclusions are the following.

In animals the assumption of a semisupine position from a supine one causes a temporary 30 per cent decrease in venous flow of the hindleg and a more protracted 10 per cent increase in arterial flow, a 2 per cent increase in flow in intestinal vessels, a 5 per cent decrease in flow in the forelimb vessels, no effect on flow in brain vessels, a 10 per cent decrease in cardiac output, a 10 per cent rise in mean blood pressure and heart rate. Following histamine the results are different in these animals, viz.: The same change in position causes a 60 per cent decrease in venous flow of the hindleg and a 25 per cent decrease in arterial flow, a 20 per cent decrease in flow in intestinal vessels, a 15 per cent decrease in flow through brain vessels, a 35 per cent decrease in flow through forelimb vessels, a 50 per cent decrease in minute output of heart, a 30 per cent decrease in mean blood pressure, and a 30 per cent increase in pulse rate. Extensive studies on man are to be found in the monograph. The author concludes that the use of the semireclining posture *with legs dependent* acts as a bloodless venesection, and this improves the circulation of the failing heart.

KATZ.

Graybiel, A.: A Consideration of the Effects of Oxygen Lack on the Cardiovascular System From the Viewpoint of Aviation. *J. Aviation Med.* 12: 183, 1941.

The degree of anoxia intentionally encountered under present flying conditions in civil and military aviation does not damage the normal heart. The changes observed in the electrocardiogram do not indicate heart injury; they are probably due in part to the alkalosis resulting from overventilation.

Heart failure of the congestive or anginal type has been produced in patients with severe degrees of heart disease on exposure to oxygen tensions simulating altitudes of 14,000 to 20,000 feet or higher.

In a total of 7 million passengers carried by five major airlines only three deaths occurred aloft; the cause in each case was ascribed to heart failure. Of five deaths known to have occurred shortly after the passengers deplaned, two were the result of heart failure. Information in regard to lesser attacks of heart failure is inadequate, but there is good reason for believing such instances are not numerous.

The general rule that "if you can walk, you may fly" has proved satisfactory in practice. Passengers with well-compensated heart disease need not hesitate to fly at the highest altitudes now flown in commercial aviation provided that an additional supply of oxygen is used. However, patients with severe valvular disease, with easily provoked angina pectoris, or who have recently had congestive failure, as well as those who are old and feeble, might well be advised against traveling by air.

AUTHOR.

Gross, F., and Matthes, K.: Venous Pressure in Man. Arch. f. Kreislaufforsch. 8: 175, 1941.

Venous pressure was recorded optically. The venous pulse of the cubital vein followed the arterial except for notching at the time the jugular pulse collapsed. This may be due to direct impact or to open arteriovenous anastomoses. Respiratory fluctuations also were present due to variations in venous flow to the heart. Marked variations in venous pressure as in Valsalva experiments were associated with variations in blood content of the skin (as measured with transillumination recorder and photoelectric cell).

KATZ.

Dressler, M., and Moskowitz, S. N.: Fetal Electrocardiography and Stethography. Am. J. Obst. & Gynec. 41: 775, 1941.

Forty gravidas were studied routinely in the last two months of pregnancy, to determine the diagnostic significance of the fetal electrocardiogram and the fetal stethogram, separately and simultaneously, in evaluating the presence of a viable fetus. The individual value of each method was enhanced by the combined study.

The fetal stethogram was positive in 100 per cent of the cases; the fetal electrocardiogram, in 80 per cent.

The stethogram is helpful in studying the rate, rhythm, and regularity of fetal heart sounds, the systolic and diastolic phases, murmurs, the uterine souffle, and fetal movements. The intensity of the fetal heart sounds depends upon the site at which the microphone is applied and upon maternal and fetal conditions. In most cases the second sound is louder than the first. As a rule, diastole is longer than systole, but in the presence of fetal tachycardia they may become equal.

The electrocardiogram is valuable in the presence of positive tracings. The absolute diagnosis of fetal presentation is made by the fetal electrocardiogram. If the waves are negative, a vertex presentation is present; if positive, a breech presentation is present. In the presence of an equal systolic and diastolic phase, the first sound is recognized by its relationship to the R-wave of the fetal electrocardiogram.

AUTHORS.

Bayer, O., and Wasmuht, K.: The Duration of the Q-T Interval in Absolute Arrhythmia. Arch. f. Kreislaufforsch. 7: 309, 1940.

The duration of electrical systole was measured in fifty-eight cases of myocardial disease with grossly irregular rhythm. In only nine instances was the duration of systole outside the expected range, and in only four of these was there no explanation for the lengthening. This study confirmed the constancy of the relationship of electrical systole to heart rate. This relationship is unchanged when the irregular heart action changes to a regular sinus rhythm. The most important factor determining electrical systole is thus the heart cycle duration.

KATZ.

Dungern, M.: Alterations in Duration of Isometric Contraction, Ejection Time, Systole and Q-T Interval. Arch. f. Kreislaufforsch. 8: 52, 1941.

After moderate exercise, the relative durations of electrical (Q-T) and mechanical (first to second sound) are shortened. (The use of the maximum amplitude of the first heart sound as the time at which ejection begins which the author employs is not always an accurate criterion. L. N. K.)

After injection of Ca intravenously in therapeutic amounts, a slowing of rate and relative shortening of mechanical systole which is not so marked as the shortening of electrical systole occur.

KATZ.

Wendt, L.: S-T Depression as a Sign of Anaerobic Cardiac Metabolism. Arch. f. Kreislaufforsch. 8: 74, 1941.

Anoxemia and insulin can cause an S-T depression. Stimulation of the vagus also causes an S-T depression. S-T depression is considered to indicate a decrease in the potential energy of the heart with a decrease in oxidative and an increase in the anaerobic metabolism. (This is a lengthy, polemical discussion.)

KATZ.

Albers, D., and Bedbur, W.: Physiological Variations in the Duration of the Ventricular Electrocardiogram. Arch. f. Kreislaufforsch. 8: 150, 1941.

This is an analysis of the literature, and 2,000 electrocardiograms of the author's were used in the study. The author considers that Q-T duration equals, on the average, $3.75 \sqrt{\text{cycle length}}$. $QRS = 0.92 \sqrt{\text{cycle length}}$. S-T (from end of QRS to end of T) $= 2.83 \sqrt{\text{cycle length}}$. S-T lengthens with age, the factor being 0.004 (age-45).

KATZ.

Stroud, W. D., and Wagner, J. A.: Silent or Atypical Coronary Occlusion. Ann. Int. Med. 15: 25, 1941.

The explanation of painless infarction is difficult. Possibly the symptoms which patients experience, such as swallowing, choking, gagging or dyspnea, may be pain equivalents. Possibly the nerve supply about the coronary vessels is different; or are they members of the hyposensitive group described by Libman?

From a therapeutic standpoint, it seems to be extremely important to be cognizant of the possibility of coronary occlusion and myocardial infarction in the absence of pain. Vagus symptoms of weakness, etc., in patients with hypertension or the onset of increased dyspnea, together with progressive failure in patients with previous mild failure, should make one alert to this serious condition. Putting the patient to bed and checking with serial electrocardiograms seem highly desirable.

The corollary may be equally true. Any patients with the typical pain of coronary insufficiency but no other suggestive clinical findings, even in the absence of changing T-waves in the electrocardiograms, must be considered as possible cases of coronary occlusion without myocardial infarction and treated accordingly. This means total bed rest for a week or ten days as a myocardial infarction might be developing. In these instances, clinical judgment is of much more importance than the electrocardiograms.

AUTHORS.

Laufer, S. T.: Subacute Myocardial Infarction or Necrosis. *Canad. M. A. J.* 45: 236, 1941.

Myocardial necrosis without typical symptoms or an acute onset, which can be detected by delayed electrocardiographic changes of coronary occlusion type, is described as a clinical entity under the title of subacute myocardial infarction or necrosis.

The mechanism of its production and the clinical symptoms and signs, justifying it as an entity, are discussed. The symptoms are so atypical that the patient often continues his regular activities, to his own detriment.

The delayed appearance of electrocardiographic changes are in accord with the clinical picture and may be discovered only accidentally some time later.

The importance of a careful history in aiding the detection of cases of subacute myocardial infarction or necrosis is strongly stressed.

A raised leucocyte count may be the only positive sign in the cases outlined.

AUTHOR.

Klemperer, P., Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus. *Arch. Path.* 32: 569, 1941.

Disseminated lupus erythematosus is founded morphologically on a well-defined series of alterations of the collagenous tissues. The characteristic organic changes, previously considered as heterogeneous, can now be understood as local manifestations of the widespread damage of collagen. Various concepts of lupus erythematosus as a disease with predominant localization in a single organ or as a diffuse disease of the peripheral circulation can be entertained no longer.

AUTHORS.

Gorenberg, H., and McCleary, J.: Rheumatic Heart Disease in Pregnancy. *Am. J. Obst. & Gynec.* 41: 45, 1941.

Three hundred forty-five cases of pregnancy complicated by rheumatic heart disease are reported.

Seventy-seven cardiac failures occurred in this group, an incidence of 22.3 per cent. It is possible to foretell fairly accurately which patient with heart disease will fail unless adequate bed rest is enforced. Several prognostic aids are offered.

The functional capacity of the heart in the nonpregnant state is of great importance, 83 per cent of the failures occurring in the badly incapacitated groups, 2B and 3, while only 17 per cent of the failures were in the comparatively well-functioning Classes 1 and 2A.

An equally important aid is the patient's age; 42.6 per cent of the pregnancies in women over 30 years of age were complicated by cardiac failure as compared to 16.1 per cent in the group under 30.

A third significant aid in prognosis is the presence or absence of a history of previous failure. Of those that decompensated before, 75 per cent had cardiac failure when pregnant as compared to a 14.1 per cent incidence of cardiac failure in the previously compensated group.

The authors feel, therefore, that the patient whose measure of functional capacity places her in the relatively severe grades of heart disease, the cardiac patient who is more than 30 years of age, the cardiac patient who gives a history of previous decompensation, should be willing, if she wishes to assume the burden of pregnancy, to submit to frequent antenatal observations from the very beginning of her pregnancy and she must be willing and able to spend the greater part of the pregnancy at absolute bed rest if necessary. The number of pregnancies borne by women with rheumatic heart disease, in itself, is apparently of no consequence. The multigravid, however, will more commonly fall into one or more of the three groups mentioned above.

The incidence of cardiac failure in pregnancy can be reduced markedly if the general principle of early and absolute bed rest is followed. The authors had two failures in their last 103 cases, and one of those was possibly preventable.

Eighty per cent of the seventy-seven cardiac failures that were seen at this hospital occurred before the last month of gestation. Acute failure during labor is a rarity. Clinical experience follows very closely the physiologic changes which indicate that pregnancy exerts a steadily increasing circulatory burden, beginning when the pregnancy begins and reaching a maximum during the eighth month. A lightening of this circulatory load occurs during the period four to six weeks preceding delivery with a consequent clinical improvement. Therefore, it is unwise to resort to late pregnancy terminations and follow the general rule of allowing the gestation to go to term.

Each pregnancy presents an individual problem in the management of labor. In this series, 8.4 per cent of the patients were delivered by the abdominal route and 91.5 per cent were delivered vaginally. Since the incidence of morbidity, as expressed by fever with its concomitant elevation in pulse rate, and the mortality rate are significantly higher following cesarean section, and since cardiac decompensation is a rare accident during labor, the "burden of proof" lies with cesarean section. This consideration applies only to section for the cardiac condition per se. Patients who have had the benefit of treatment and go into labor well compensated may in general be handled on the basis of obstetric indication, essentially as though not suffering from heart disease.

AUTHORS.

Hannesson, H.: Tuberculosis of the Pericardium and Heart. *Tubercle* 22: 79, 1941.

Involvement of the pericardium by a contiguous or neighboring tuberculosis is not so rare as is generally supposed. Tuberculosis limited to the pericardium is rare. Invasion of the pericardium from tuberculosis of the pleura, mediastinum, or thoracic vertebrae is observed from time to time. In miliary tuberculosis tubercles may be demonstrated in the myocardium at autopsy although their presence cannot be detected clinically.

Tuberculosis of the pericardium is usually a fatal disease, but, in the event that the tuberculous process in the pericardium and elsewhere in the body subsides, the mechanical effects on the heart are a result of pericardial healing. The inflammatory process heals with resulting cohesion of the visceral and parietal layers of the pericardium, so that partial or complete obliteration of the sac occurs. This condition imposes extra work on the heart and results in cardiac hypertrophy and in some cases in ultimate heart failure.

If the pericarditis is extensive and particularly if there is an associated mediastinitis, the resulting fibrosis may greatly hamper the right auricle and the great veins, particularly the inferior vena cava, so that the return of blood to the

heart is partially obstructed. This results in congestion of the liver, which becomes chronic and causes recurrent ascites. This condition is called chronic mediastino-pericarditic pseudocirrhosis of the liver or Pick's disease.

Post-mortem statistics indicate that probably no serious disease is so frequently overlooked as one that affects the pericardium. Tuberculosis of the pericardium is not a rare condition. The terms anatomically primary and clinically primary tuberculous pericarditis are unsatisfactory. The occurrence of anatomically primary tuberculous pericarditis is questioned. The pericarditis is probably always secondary to some other tuberculous lesion. Most instances of tuberculosis of the pericardium are due to a retrograde extension of the infection through the lymphatic channels from a mediastinal focus. In place of the term clinically primary tuberculous pericarditis, it is suggested that cases of tuberculous pericarditis be divided into (1) those in which the pericarditis was the most important factor in the production of the clinical picture and (2) those which occur during the course of a disseminated tuberculosis.

Tuberculosis of the pericardium occurs most often in males over 40 years of age. The colored race appears to be more susceptible to the disease than the white race. The proof of the tuberculous nature of a pericardial effusion may be extremely difficult to obtain. Inoculation of a guinea pig is often necessary. The prognosis of tuberculous pericarditis is bad. The mortality in two series reported in the literature is given as 83 per cent in both instances. Present methods of treatment of tuberculous pericarditis are unsatisfactory. In the healed state tuberculous pericarditis presents the histologic picture of a nonspecific fibrous pericarditis. Pick's disease has often been found to follow tuberculous pericarditis. Polyserositis is probably tuberculous in origin and is a condition associated with a high degree of immunity to the infection. Tuberculosis of the myocardium, endocardium, and blood vessels is rare. It is difficult to determine any exact relationship between pulmonary tuberculosis and diseases of the heart.

AUTHOR.

Koons, R. A., and Kissane, R. W.: The Incidence of Heart Disease in Children With Congenital Syphilis. Urol. & Cutan. Rev. 44: 673, 1940.

The relative incidence of heart disease in congenitally syphilitic children closely approximates the incidence of congenital syphilis in known cardiac children.

The incidence of heart disease in congenitally syphilitic children is too small to permit consideration of syphilis as an etiological factor in the production of congenital heart disease.

The association of rheumatic heart disease and congenital heart disease is incidental.

Congenital syphilis can practically be disregarded as the etiological factor in any type of heart disease in children.

AUTHORS.

Friedman, M., Sugarman, H., and Selzer, A.: The Relationship of Renal Blood Pressure and Blood Flow to the Production of Experimental Hypertension. Am. J. Physiol. 134: 493, 1941.

The renal hemodynamics and systemic blood pressure were studied following aortic constriction above and between the renal artery aortic orifices.

It was found that renal ischemia is not necessary for the initiation or maintenance of a chronic (renal) experimental hypertension.

AUTHORS.

Leary, T.: *The Genesis of Atherosclerosis*. Arch. Path. 32: 507, 1941.

From the evidence accumulated and presented, the author points out that atherosclerosis in man and in the experimental rabbit is due to the presence of excess cholesterol esters within phagocytic cells, which first appear in the intima of the arterial wall. The cholesterol is esterified in the liver as directly observed in the experimental rabbit. The cholesterol when fed in excess to rabbits is deposited in the form of esters in the cells of the liver and adrenals. The esters as they accumulate in excess become a burden and are removed from these organs by Kupffer cells in the liver and their analogues in the adrenals. The cholesterol esters are engulfed as particulate matter by these cells. These cells, now lipid cells, escape from the liver and adrenals through the blood and lymph systems and may produce obstruction in the lymph sinuses. The lipid cells, having entered the blood stream, pass through the lung filter and selectively invade the arterial intima. This invasion is favored by stresses but is apparently dependent on a positive chemotaxis of the arterial wall for cells carrying cholesterol esters. The latent period after the beginning of cholesterol feeding in the rabbit and before aortic lesions appear is dependent on the production of esters in excess and their transport, as indicated in paragraphs 2 and 7 inclusive. The lipid cells possess the power to split cholesterol esters and bring the substance into solution in an excess of fatty acids. The excess cholesterol esters are akin to silica in their irritant character. Both are difficult of metabolism, tend to stay long in tissues and stimulate a growth of connective tissue. The intravenous silica and cholesterol esters, practically alone among particulate matters, tend to cause in rabbits cirrhosis of the liver, enlargement of the spleen and changes in the kidneys resembling those of chronic "interstitial" nephritis. The human atherosclerosis is associated with intermittent accretions of excess cholesterol esters in contrast to the continuous accretions in the rabbit fed cholesterol. That the differences in the appearance of atherosclerotic lesions in the two species are due in great part to differences in the manner of feeding. Diffuse lipoidosis is more common in the experimental rabbit, partly for the same reason.

The accepted criteria for the establishment of a causal relation between a given agent and a disease are embodied in Koch's laws. Since animals are not susceptible to all human infections, or because evident parasites cannot be cultivated, or for other reasons, various compromises have been made with these postulates. However, the evidence of a casual relation is most complete when Koch's laws can be satisfied.

In the causation of atherosclerosis the principles of Koch's laws can be fulfilled. Excess cholesterol is always present in the active stages of human atherosclerosis. It can be identified in the lesions as definitely as can the bacterial or other parasitic agents producing infections. It can be extracted from the lesions. Human arterial lesions can be reproduced experimentally by its use with more exactness than the lesions of many human infections can be reproduced by the introduction into susceptible animals of their recognized causal agents. It can be identified in and extracted from the experimental lesions.

Stresses determine the localization of lesions and influence the degree of the sclerotic processes. The efficiency of cholesterol metabolism is modified by sex and thyroid factors. Age (time plus thyroid deterioration) and heredity are also contributing elements.

AUTHOR.

Schleicher, I.: *The Story of the Coronary Arteries*. Anatomy, Pathology, Physiology, and Functional Pathology. Arch. f. Kreislaufforsch. 8: 17, 1941.

This is an historical review of the coronary arteries which assembles the earlier literature on this subject adequately but neglects to some extent recent American work on the subject.

KATZ.

Feil, H., and Beck, C. S.: Coronary Sclerosis and Angina Pectoris. *J. Thoracic Surg.* 10: 529, 1941.

The authors present a follow-up report on patients who had vascularized grafts placed upon the heart for the purpose of producing a collateral blood supply to the heart. Of the thirty patients operated upon, thirteen (65 per cent of those surviving) were definitely improved. Their clinical symptoms were either completely or almost entirely relieved, so that they could resume their previous occupations. Four patients (20 per cent of those surviving) were moderately improved, while in three instances (15 per cent of those surviving), there was inconsequential improvement. An anatomic study of three specimens was made. In one of these, the clinical result had been good and the specimen showed vascular anastomoses. In this group of twenty surviving patients, the high percentage of patients showing great improvement is not only significant but encouraging. This statement may be emphasized because all of these patients were seriously disabled before the operation.

AUTHORS.

Reid, L. C.: Anesthesia in Relation to Cardiac Disease. *Anesthesiology* 2: 161, 1941.

All anesthetic agents and most alkaloids inhibit the enzymes, dehydrogenases, which form such an important link in the chain of events which gives rise to the production of energy by the cell. This accounts, in part at least, for the hyperglycemia during anesthesia as well as decreased carbon dioxide build-up and various degrees of failure of cellular function.

A high vitamin B content in the diet is necessary to assure an adequate supply of respiratory carriers such as flavoprotein, and nicotinic acid amide, as well as thiamin. Accordingly, the diet, preoperatively, becomes of the greatest importance to the anesthetist.

Irritation of the respiratory tract or esophagus may set up vagovagal reflexes with resulting derangement of cardiac and respiratory activity, and all such contemplated procedures, as the introduction of tubes, catheters, etc., should be covered by adequate preoperative therapy to minimize or actually prevent the undesirable reactions potentially present in autonomic reflexes.

Every operative case during the menopause which shows any cardiac symptoms or signs, or electrocardiographic findings suggestive of cardiac lesions, should have the benefit of an adequate course of estrin substitution therapy.

AUTHOR.

Lindner, E., and Katz, L. N.: Further Observations on the Action of Drugs on the Caliber of Coronary Vessels. *J. Pharmacol. & Exper. Therap.* 72: 306, 1941.

The digitalis derivatives, K-strophanthin, ouabain and digifoline at times have a direct coronary constrictor action even in therapeutic doses.

Metrazol and glucose are mild, direct coronary dilators.

Calcium gluconate, in contrast with the chloride salt which is a powerful dilator of the coronary vessels, does not cause any constant or striking change in coronary caliber except that a mild dilatation occurs with large doses.

Aminophyllin and caffein sodium benzoate are consistently direct coronary dilators, the aminophyllin being the more powerful.

Papaverine hydrochloride is a powerful long-lasting direct coronary dilating agent. This and its tendency to prevent ventricular fibrillation probably explain its clinical benefits.

AUTHORS.

Riseman, J. E. F., and Linenthal, H.: The Prolonged Use of Enteric-Coated Tablets of Theobromine Sodium Acetate in the Treatment of Edema and Angina Pectoris. *New England J. Med.* 224: 933, 1941.

Enteric-coated tablets of theobromine sodium acetate and theophylline sodium acetate are now available, which make it possible to give therapeutically adequate doses of these drugs over long periods. By this means, the necessity of intravenous administration of diuretics may be obviated or decreased in certain patients with heart disease or nephritis, and the frequency and severity of attacks of angina pectoris may be diminished. When the drugs have been given continuously for a long time, no untoward effects have been observed except for occasional slight gastric discomfort. The optimum dosage for most patients appears to be 0.5 Gm. of enteric-coated theobromine sodium acetate, or 0.2 Gm. of enteric-coated theophylline sodium acetate, given four times daily, before meals and before retiring. Adequate dosage is necessary; in angina pectoris it is especially important to administer a dose of the medication before retiring.

AUTHORS.

Wedd, A. M., Blair, H. A., and Dwyer, G. K.: The Effect of Digoxin on the Cold Blooded Heart and Its Bearing on the Mechanism of Digitalis Action. *J. Pharmacol. & Exper. Therap.* 72: 394, 1941.

The effect of digoxin has been studied on spontaneously beating strips of auricle from the frog, *Rana pipiens*, and the turtle, *Pseudomys elegans*, and rhythmically driven strips of ventricle from the turtle. The spontaneous rhythm was usually slowed markedly by the drug. Measurements were made on the driven strips of the Q-T interval, the conduction time, the maximal tension, the duration of systole, the effect of a single short diastole on the ensuing Q-T, the effect of different rates on Q-T, the relation of Q-T to the duration of systole and variations of the threshold to electric stimuli. Mechanical systole is proportional to electrical systole, and both are invariably shortened by the drug. The shortening is less at higher rates of beating because the Q-T of a given tissue cannot be shortened beyond a certain limit, either by single early beats or rapid driving, and this limit is the same with or without the drug. Since the refractory period which is equal to Q-T is shortened by the drug and the threshold does not regularly change markedly, the slowing action of the drug is ascribed to the slowing of the development of excitation at the pacemaker region. Slowing of conduction usually occurred but later than Q-T changes. Tension increases were irregular and, when seen, occurred early. The amplitude of contraction may be independent of the duration of systole and the diastolic interval. The possible significance of the shortening of systole for the therapeutic action of digitalis was discussed briefly. It seems reasonable to suppose that the final action of digitalis is related to the lengthened diastole which it produces. There is reduction in the maintenance energy requirement, and longer time for recovery from contraction is given.

AUTHORS.

Cattell, M., and Gold, H.: Studies on Purified Digitalis Glucosides. III. The Relationship Between Therapeutic and Toxic Potency. *J. Pharmacol. & Exper. Therap.* 71: 114, 1941.

The relative potency with regard to both therapeutic and toxic effects on isolated papillary muscles from the cat have been determined for the following glucosides: ouabain (Merck), digitoxin (Merck), digitaline (Laboratoire Nativelle), lanatoside A (Sandoz), lanatoside B (Sandoz) and lanatoside C (Cedilanid, Sandoz).

The minimum concentration of ouabain and digitoxin, i.e., that causing increased force of contraction in 50 per cent of experiments (therapeutic effect) is 1 part in 100 millions of Locke's solution; for the lanatoside compounds it is approximately 1 part in 10 millions.

When the concentration of any of the glucosides is sufficiently increased, toxic effects are produced, including extra contractions, loss of excitability, and diminished force of contraction.

The ratio of the concentrations producing therapeutic and toxic effects is the same for "digitaline nativele" and ouabain. There is also similarity among the several lanatoside glucosides studied, and thus by this technique we have not been able to confirm the wide margin between the therapeutic and toxic dose reported by Moe and Visscher for lanatoside C.

Ouabain and "digitaline nativele" both give a slightly higher value for the ratio of toxic to therapeutic concentration in comparison with the lanatoside compounds. The evaluation of the significance of this finding must await further evidence.

The available evidence pertaining to the questions of differences in the relationship between toxic and therapeutic doses among different glucosides is discussed, and the conclusion is reached that proof of the existence of such differences is still wanting.

AUTHORS.

Boyd, L. J., and Scherf, D.: The Electrocardiogram in Acute Emetine Intoxication. *J. Pharmacol. & Exper. Therap.* 71: 362, 1941.

The alterations of the electrocardiogram after the intravenous administration of emetine hydrochloride were studied in dogs and cats.

Disturbance of intraventricular conduction is the most common change observed under these circumstances. Bradycardia and prolongation of atrioventricular conduction time develop regularly, but they are not pronounced.

If the intravenous dose does not exceed 37 mg. in dogs weighing 5 to 9 kg., the electrocardiographic alterations gradually disappear within forty-five minutes. Cardiac dilatation, especially involving the right ventricle, the development of which is simultaneous with the ventricular conduction disturbances, also vanishes within the same period.

The action of emetine is cumulative since much more pronounced effects result from the second or third injection of an equal amount of the drug although the normal electrocardiogram had been restored.

The most common arrhythmias to develop are auricular extrasystoles and auricular tachycardias. Alternation of the ventricular complexes is frequently observed during the tachycardia. Advanced stages of intoxication are required for the production of ventricular extrasystoles. Heart block with dropped beats was encountered only in cats.

AUTHORS.

Hildebrandt, F.: The Action of Strophanthin on the Blood Vessels. Arch. f. Kreislaufforsch. 8: 137, 1941.

This is a summary of recent literature including studies published by the author. The decrease in cardiac minute output is due to constriction of the blood vessels in the skeletal muscles and gut and of the veins leaving the liver. The constriction of the renal vessels is less marked and fleeting. The cerebral vessels dilate. The coronary vessels constrict if the heart is not damaged but dilate when it is damaged and this dilatation parallels the work of the heart.

KATZ.

In Memoriam

WALTER W. HAMBURGER

1881-1941

Walter Wile Hamburger was born in Chicago on September 10, 1881, the son of Max and Annette (Wile) Hamburger. He received his B.S. degree at the University of Chicago in 1903, his M.S. in 1904, and his M.D. degree at Rush Medical College in 1906. He served his internship at the Presbyterian Hospital, in Chicago, from 1907 to 1908. The following fourteen months (1908-1909) Dr. Hamburger did postgraduate study in pathology and internal medicine in Berlin, Munich, and Vienna, including the clinic of Friedrich Kraus at the Charity Hospital, Berlin, and the clinic of Friedrich Mueller, in Munich. He was assistant to the late Dr. Frank Billings for three years, and then began the private practice of medicine, specializing in internal medicine.

Dr. Hamburger was Assistant Clinical Professor in Medicine at Rush Medical College from 1914 to 1934, and was Clinical Professor of Medicine at the University of Chicago from 1934 to the time of his death. He was a member of the Staff of Cook County Hospital from 1913 to 1926. He was Attending Physician at Michael Reese Hospital from 1912 to 1925, and then became Senior Attending Physician. He was Chief of Staff of Michael Reese Hospital during the years 1928 and 1929. He was a Major in the Medical Corps, United States Army, from 1917 to 1919, and was Chief of the Medical Service of the Base Hospital at Camp Zachary Taylor, Louisville, Kentucky.

Dr. Hamburger, in 1915, became a Charter Member of the Institute of Medicine of Chicago and served on its Executive Committee and Board of Governors until the time of his death. He was a member of the American Society for Clinical Investigation, the Society for Experimental Biology and Medicine, the Central Society for Clinical Research, and the American Board of Internal Medicine. He was a member of the Board of Public Health Advisors of the Illinois State Department of Public Health, and was an emeritus member of the Association of American Physicians and of the Chicago Society of Internal Medicine. He belonged to the American Medical Association, the Chicago Medical Society, and the Illinois State Medical Society, and was on the Advisory Board of Psychosomatic Medicine. He was a member of Sigma Xi, Phi Beta Kappa, and Alpha Omega Alpha.

Dr. Hamburger married Edna Levis, of St. Louis, Missouri, December 27, 1911, and is survived by her and their two children, Mrs. Elizabeth H. Ries and Dr. W. W. Hamburger, Jr.



WALTER W. HAMBURGER

Dr. Hamburger played a leading role in determining the policies of the Michael Reese Hospital; his was the primary responsibility for the conception, establishment, and growth of its Cardiovascular Department, and he gave this project constant and unqualified support, though quietly keeping in the background. He was associated with many other cardiac activities in his community. He was formerly Vice-President and later a member of the Board of Governors and the Executive Committee of the Chicago Heart Association. He was a member of the Medical Advisory Board of the Sunset Camp for Convalescent Cardiac Children.

His interest in heart disease was evident in his publications. He contributed over 100 articles on internal medicine to medical journals, with particular reference to the heart and circulation. He was the author of a chapter on "Cardiac Arrhythmias" in Cecil's *Textbook of Medicine*, and of the chapter on "Gastro-Intestinal Manifestations of Cardiovascular Disease" in Portis' *Diseases of the Digestive System*. Dr. Hamburger was a member of the American Heart Association, in which he held the office of Treasurer, and was a member of the Executive Com-

mittee for many years; until 1938, he served on the Advisory Editorial Board of the AMERICAN HEART JOURNAL.

The sudden and unexpected death of Dr. Walter W. Hamburger came as a shock. It deprived the medical profession of an outstanding practitioner who was devoted to his patients, a courageous supporter of advances in medicine and public health, a scholar who placed on record many contributions which are notable for their modesty and scientific spirit. His absence will be noticed particularly in the field of cardiology, to the advancement of which he contributed greatly and in many ways.

The loss of Dr. Hamburger seems irreparable, but those of us who were his friends console ourselves that the spirit of this gentle, lovable, and scholarly man will live on.

LOUIS N. KATZ.

KAREL FREDERIK WENCKEBACH

1864-1940

A short time ago news arrived from Vienna, rather belatedly, that Karel Frederik Wenckebach had died last winter at the age of 76. A great physician, a distinguished scientist, a stimulating teacher, a cultured scholar had passed away.

The imperishable memorial built upon the scientific studies of Wenckebach constitutes an eloquent testimonial of the lasting imprint which he stamped upon medicine. Since his scientific achievements are known to every reader of this journal, an attempt to evaluate the significance of his contributions to cardiology would be superfluous. It seems more fitting in these lines, devoted to a commemoration of Wenckebach, to describe briefly some features of his development and to delineate some traits of his personality.

Born in The Hague, Wenckebach studied medicine at Utrecht, where he became engaged in the study of embryology and hematology. The discovery that he was color-blind necessitated a change in his life plan. He turned to physiology, and spent many hours in the laboratory of Engelmann, who, at this time, was employing "the method of extra-systole" in studies of the fundamental properties of the heart. The opportunity to observe these frog experiments proved decisive in Wenckebach's further development.

Subsequently, economic circumstances compelled him to leave the University and enter practice in a small Dutch village. Wenckebach often referred to this period with great satisfaction, and emphasized the diversity of problems which a country practitioner encounters and the difficulties under which they must be solved. Among his daily duties was supervision of the medical care in a home for the aged. This was extremely fortunate, for many of the charges had disturbances of cardiac rhythm. One day, while auscultating a patient, Wenckebach found a

strange arrhythmia which reminded him of the irregular movements of the lever he had seen so frequently in Engelmann's laboratory. Wenckebach loved to relate how the patient had told others in the ward that "the doctor had fallen asleep on my chest," for Wenckebach had listened for an unusually long time to that heart. An analysis of sphygmograms recorded on this and other patients permitted Wenckebach to describe extrasystoles for the first time in man (1898). His discovery of periodic dropped beats, often called Wenckebach's periods, followed soon thereafter. Their recognition by an analysis of sphygmograms is likewise a remarkable achievement when one recalls the crude apparatus then available. This work was followed by a study of pulsus alternans, and, in 1903, the first complete description of his research appeared in the form of a monograph.



KAREL FREDERIK WENCKEBACH

Two years earlier Wenckebach had given up his practice to accept a position at the University of Groningen, in Northern Holland, where he was entrusted with the direction of the medical division.

During the succeeding years his scientific development was profoundly influenced by the friendship of Sir James Mackenzie and Sir Arthur Keith. For example, by means of venous pulse tracings, registered with the Mackenzie technique, he discovered the first cases of dropped beat when conduction time remained fixed (1906). The Keith influence is

reflected in his work during the next four years, which were devoted to important investigations of the interrelation between circulation and respiration and to his classical study of pericarditis with effusion and adhesive pericarditis.

In 1911, Wenckebach was appointed Head of the Department of Medicine at the University of Strassburg, and, in 1914, he accepted the responsibility for the First Medical University Clinic in Vienna. He remained in this post until his voluntary retirement from official duties, at the age of 65, in 1929.

In 1914 a completely revised edition of his famous book appeared. Actually, it was practically a new work, and more important than its predecessor. During the same year he published a report of the beneficial effect of quinine in certain arrhythmias which established the clinical basis for this and allied compounds in cardiac therapeutics. With characteristic honesty, Wenckebach acknowledged that he became aware of the effect of quinine on disturbances of stimulus formation when one of his patients made the suggestion after careful self-observation. Although the second edition of his book contained many fundamental observations on various important arrhythmias, there was only one electrocardiogram in it. This was the last important book dealing with disturbances of cardiac rhythm based exclusively upon smoked-paper tracings.

Fully aware of the importance of electrocardiography, Wenckebach decided to obtain the assistance of Winterberg in the preparation of a new edition of his book. Six years were occupied in its preparation, and the monumental volume, *The Irregular Action of the Heart*, was published in 1927, with Winterberg as coauthor.

The case histories shown to him by his pupil Aalsmeer aroused Wenckebach's interest in the circulatory disturbances encountered in beriberi. The resultant scientific expedition to the Dutch East Indies accomplished much, and the observations were published in a monograph. These observations constituted the foundation for the recognition of non-tropical beriberi as it is seen in the United States.

It will be noted that his list of publications is not long, but each represents a distinct contribution. He objected decidedly to the writing of superfluous scientific papers, which he regarded for the most part as "pseudoscientific secretion," to employ his own term.

As Professor of Internal Medicine and Head of the First Medical Clinic, he brought this institution to its high position and did much to enhance its reputation as one of the outstanding European medical centers. He was a master of physical diagnosis. This quality, combined with his deep insight into human character, his tact, and a thoroughly optimistic attitude, made him one of the best known consultants on the continent. His practice extended far beyond the borders of little post-war Austria. In his clientele were found many of the important figures who guided the destiny of their respective countries.

Presumably some of these facts influenced his attitude toward "full-time teachers," for he was accustomed to emphasize the great importance of private practice for the research worker and for those entrusted with the teaching of medical students. He believed that private practice provided a more ample opportunity to study material and a wider range of material than is available to the physician who limits his activities to hospitalized patients.

It was rather typical of Wenkebach that each new patient immediately awakened a great interest, and the subsequent therapeutic success pleased him like a new result, although he had seen it happen thousands of times. This optimism, his real joy in therapeutic accomplishment, and his unusual charm, coupled with a complete lack of affectation or ostentation, immediately impressed everyone in contact with him.

It was one of his great regrets, to which he often gave voice, that he had been unable to accept an invitation of Sir William Osler to visit the United States. In 1923, however, he was asked to deliver the Harvey Lecture in New York and the Herter Lecture in Baltimore. He utilized this opportunity to visit many of his American friends and to study many medical institutions in this country. His impressions were published in an interesting paper, "What We Can Learn From America" (*Wien. klin. Wchnschr.* 37: 217, 1924). Reference may be made to one point touched upon in that paper. He recognized the rapidly increasing importance of American developments in medicine, and, in an almost prophetic manner, urged his colleagues to added scientific efforts lest medicine in Vienna lag behind and become outdistanced by American medical achievements.

Wenkebach's life was a happy one. His rise from an obscure general practitioner in an unimportant village to one of the highest medical positions in Europe was well deserved. It was his good fortune, while still in the prime of life, to become one of the most famous physicians of Europe, and to see his scientific work recognized among fellow workers, as evidenced by honorary memberships in some of the most distinguished medical societies in the world. It was fortunate that he was permitted to serve humanity so long and so fruitfully. It was also a happy circumstance that he was able to continue his activities almost to the end of his long life. Although afflicted with a disease characterized by a prolonged and painful course, the closing phase was marked by serenity and peace.

DAVID SCHERF.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. PAUL D. WHITE
President

DR. ROY W. SCOTT
Vice-President

DR. T. HOMER COFFEN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

*DR. EDGAR V. ALLEN	Rochester, Minn.	*DR. EDWIN P. MAYNARD, JR.	Brooklyn
DR. T. HOMER COFFEN	Portland, Ore.	*DR. THOMAS M. McMILLAN	Philadelphia
DR. CLARENCE DE LA CHAPELLE	New York City	DR. JONATHAN MEAKINS	Montreal
DR. WILLIAM DOCK	San Francisco	DR. E. STERLING NICHOL	Miami
DR. HUGH FARRIS, St. John, N. B., Canada		DR. FRANKLIN R. NUZUM	Santa Barbara
DR. NORMAN E. FREEMAN	Philadelphia	*DR. STEWART R. ROBERTS	Atlanta
DR. GEORGE R. HERRMANN	Galveston	*DR. ROY W. SCOTT	Cleveland
DR. T. DUCKETT JONES	Boston	DR. FRED M. SMITH	Iowa City
*DR. WILLIAM J. KERR	San Francisco	*DR. HOWARD B. SPRAGUE	Boston
DR. EMANUEL LIBMAN	New York City	DR. WILLIAM D. STROUD	Philadelphia
DR. DREW LUTEN	St. Louis	*DR. PAUL D. WHITE	Boston
DR. GILBERT MARQUARDT	Chicago	DR. FRANK N. WILSON	Ann Arbor
*DR. H. M. MARVIN	New Haven	*DR. IRVING S. WRIGHT	New York City
		DR. WALLACE M. YATER	Washington, D. C.

DR. H. M. MARVIN, *Chairman, Executive Committee
and Acting Executive Secretary*

GERTRUDE P. WOOD, *Office Secretary*

TELEPHONE CIRCLE 5-8000

THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-seven physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$11.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

**Executive Committee.*

INDEX TO VOLUME 22

A

- Abnormality (*see* anomaly)
- Abramson, D. I., and Fierst, S. M., 566
- , Katzenstein, K. H., and Ferris, E. B., Jr., 329
- Acetyl- β -methylcholine, auricular fibrillation in normal intact animals after intravenous injection of, 47
- chloride, injection of, auricular fibrillation following, during attack of paroxysmal auricular tachycardia or flutter, 425*
- Acetylcholine, observations on production of myocardial disease with, 116
- Acidosis, diabetic, peripheral circulatory failure in, and its relation to treatment, 564*
- Age, process of, in animal body, significance of tensility of aorta as index of, 661
- Aged (*see* old age)
- Aggeler, P. M., Lucia, S. P., and Thompson, J. H., 825
- Albers, D., and Bedbur, W., 841*
- Allen, Edgar V., and Leary, W. V., 719
- Allergy, insulin, case of, simulating coronary occlusion, 280*
- Altschule, M. D., and Iglauer, A., 430*
- , —, and Davis, D., 47
- American Heart Association, announcement, 140
- Aminophylline, effectiveness of, in treatment of angina pectoris, 576*
- Andrus, E. C., and Hill, W. H. P., 423*
- Anesthesia, choice of, in operative patient with heart disease, 285*
- in relation to cardiac disease, 846*
- spinal, effects of, application of formulae for afferent and efferent arteriolar resistance in human kidney, 571*
- Aneurysm aortic, dissecting, spinal cord ischemia in, 305
- arteriosclerotic, and senile ectasia of thoracic aorta, 458
- intrapericardial aortic, 569*
- mycotic, ruptured aortic valve with, due to acute bacterial endocarditis, 426
- of aorta, abdominal, 137*
- surgical treatment of, 136*
- Angina pectoris, coronary sclerosis and, 846*
- objective evidence of efficacy of medicinal therapy in, 494
- occurrence of electrocardiographic changes in, similar in magnitude and in kind to those produced by myocardial infarction, 64

- Angina pectoris—Cont'd
- treatment of edema and, prolonged use of enteric-coated tablets of theobromine sodium acetate in, 847
- effectiveness of xanthine drugs (aminophylline) in, 576*
- octyl nitrite in, 519
- Angiotonin, "pressor," effects of renin and, cardiac factor in, 423*
- Anomaly, cardiac, "corrected transposition" and persistent rudimentary "right aorta," as evidence in support of Spitzer's theory, 568*
- incidence of rheumatic and congenital heart disease among school children of Louisville, Ky., 112
- tetralogy of Fallot, record case of, with comments on metabolic and pathologic studies, 754
- Anoxemia, induced, further observations on effects of certain xanthine compounds in cases of coronary insufficiency as indicated by response to, 252
- Aorta, abdominal, aneurysm of, 137*
- aneurysm of, surgical treatment of, 136
- aneurysm, dissecting, of, spinal cord ischemia in, 305
- coarctation of, evidence for general distribution of peripheral resistance in, 567*
- tensility of, significance of, as index of aging process in animal body, 661
- thoracic (aneurysms) arteriosclerotic and senile ectasia of, 458
- Aortitis, syphilitic, as cause of sudden death, 277*
- Arteriography, experimental, study of, 423
- Arterioles, resistance, afferent and efferent, of, formulae for, in human kidney, application to effects of spinal anesthesia, 571*
- Arteriosclerosis, genesis of, 845*
- peripheral lumbar sympathectomy in treatment of selected cases of, 75
- relation of, experimental pulmonary arterial hypertension to, 423*
- Arteritis, peripheral, tuberculous, associated with tuberculous thrombophlebitis in lungs, 702
- Artery, all, arising from aortic arch, occlusion of, syndrome of, 825
- carotid, common, internal and external, thrombosis in, 575*

An asterisk () after a page number indicates the reference is an abstract and not an original article.

Artery—Cont'd

- constriction of, and veins, effect of, induced by paredrine in lung capacity and its subdivisions, 430*
- coronary, caliber of, further observations on action of drugs on, 846*
- occlusion of, case of insulin allergy simulating, 280*
- multiple fresh, of patient with antecedent shock, 568
- of, syndrome of painful disability of shoulder and hand complicating, 1
- silent or atypical, of, 841
- temporary, experimental studies on effect of. II. Production of myocardial infarction, 374
- operation on, 539
- sclerosis, medial, of, in infancy, 132*
- of, and angina pectoris, 846*
- story of, anatomy, pathology, physiology, and functional pathology, 845*
- sympathectomy and experimental occlusion of, 545
- thrombosis of, with recovery in case of thromboangiitis obliterans, 707
- tibial artery changes in comparison with those of radial and, 573*
- disease, occlusive, chronic, of, femoral vein ligation for, 428*
- of heart and, synopsis of, 717 (B. rev.)
- dorsal metacarpal, digital, and terminal skin of hand, relative responses of, in vasoconstrictor reflexes, 574*
- large, gradual occlusion of, experimental studies on, 137*
- peripheral, major, prevention of ischemic gangrene following surgical operations upon, by chemical section of cervico-dorsal and lumbar sympathetics, 137*
- radial, tibial artery changes in comparison with those of, and coronary arteries, 573*
- renal, occlusion, partial of, unilateral kidney with, associated hypertension, 284*
- renal, occlusion, partial of, unilateral angiographic study, 423
- spasm of, intermittent claudication as result of, induced by walking, 719
- thrombosis, multiple, case of, occurring in professional donor, 427*
- tibial, changes in, in comparison with those in radial and coronary arteries, 573*

Ash, Rachel, 439

Askey, John Martin, 1

Atherosclerosis (*see* arteriosclerosis)

Atlas, Lawrence N., 75

Auricle, fibrillation of (*see* fibrillation, auricular)

Autonomic nervous system, mechanism of, heat conservation and dissipation. I. Effects of heating body; evidence for existence of capillary dilator nerves in anterior roots, 289

Aviation, consideration of effects of oxygen lack on cardiovascular system from viewpoint of, 839*

Axis deviation, characteristic electrocardiograms in left ventricular strain with and without, 279*

Ayer, G. Darrell, and Burwell, C. S., 267

B

Baehr, G., Klemperer, P., and Pollack, A. D., 842*

Baer, S., and Isard, H. J., 713*

Bain, C. W. C., 280*

—, and Wray, S., 426*

Ballistocardiography, clinical studies with, in congestive failure, on digitalis action, on changes in ballistic form, and in certain acute experiments, 712*

Barach, Alvan L., Steiner, A., Eckman, M., and Molomut, N., 13

Barber, H., and Osborn, G. R., 280*

Bayer, O., and Wasmuth, K., 841*

Bazett, H. C., Laplace, L. B., and Scott, J. C., 737, 749

Beck, Claude S., 539

—, and Feil, H., 846*

—, and Roberts, J. T., 314

—, Stanton, E. J., and Schildt, P., 529

Bedbur, W., and Albers, D., 841*

Bedford, D. E., and Lovibond, J. L., 285

Beeson, Paul B., and Levine, S. A., 401

Bellet, Samuel, and Kershbaum, A., 195

Berconsky, I., Cossio, P., and Gamba, R., 281*

Berdez, George L., Tuohy, E. L., and Boman, P. G., 305

Bernstein, Phineas, and Mann, H., 390

Bierman, W., and Lichtman, S. S., 286*

Bigger, I. A., 136*

Blackford, L. M., and Parker, F. P., 280*

Blair, H. A., Wedd, A. M., and Dwyer, G. K., 847*

Bland, E. F., and White, P. D., 281*

Blaney, Loren F., Geiger, A. J., and Druckemiller, W. H., 630

Blood flow, relationship of renal blood pressure and, to production of experimental hypertension, 844*

velocity of, correlation of, and basal metabolic rate in various metabolic disorders, 713*

gases in, physiologic action of oxygen and carbon dioxide on coronary circulation as shown by, and electrocardiographic studies, 13

Blood—Cont'd

- picture of, in rheumatic fever, 342
- pressure, estimation of cardiac output from, and pulse wave velocity measurements on subject with cardiovascular disease. I. Cardiovascular disease other than aortic regurgitation, 737
- II. Aortic regurgitation, 747
- pressure, renal, and blood flow, relationship of, to production of experimental hypertension, 844*
- stroke volume, and heart size of dog, effect of cyclopropane on, 563*
- venous, collapse factor in, flow of fluid through collapsible tubes, 562*
- in man, 840*
- responses of, to exercise, 360
- vessels, action of strophanthidin on, 849*
- coronary, communicating, effect of abrasion of surface of heart upon, 529
- intracranial, reactivity of, in aged, 427*
- Blumenthal, Basil, and Reisinger, J. A., 811
- Blumgart, Herrman L., Gilligan, D. R., and Schlesinger, M. J., 374
- , Schlesinger, M. J., and Zoll, P. M., 568*
- Boden, Erich, 433
- Bohnengel, C., 569*
- Bohning, A., Katz, L. N., and Langendorf, R., 778
- Boman, P. G., Tuohy, E. L., and Berdez, G. L., 305
- Book Reviews:
 - Cardiac classics, collection of classic works on heart and circulation, with comprehensive bibliographic accounts of authors, 578
 - Cardiac insufficiency, 577
 - Clinical aspects of electrocardiogram, 287
 - Diagnosis and treatment of cardiovascular disease, 433
 - Electrocardiography for practicing physician, 433
 - Heart disease, volume 1, physiology, examination and functional pathology of heart, 437
 - Heart in pregnancy and childbearing age, 431
 - Hypertension and nephritis, 139
 - Influence of thyroid hormone on heart and circulation, 577
 - Management of cardiac patient, 579
 - Nature therapy studies in treatment of heart, electrocardiographic studies, 436
 - Synopsis of diseases of heart and arteries, 716
 - Your heart, 716
- Boyd, L. J., and Scherf, D., 715*
- Boyd, T. E., and Patras, M. C., 561*

- Brace, D. E., Scherf, D., and Spire, L. J., 563*
- Breathing, gas-mask, influence of, on circulation of men, 427*
- Bronk, D. W., Pitts, R. F., and Larrabee, M. G., 562*
- Brown, C. E., and Richter, I. M., 132*
- Brown, Edward E., Wasson, V. P., and Weintraub, C., 342
- Browning, J. S., and Clark, C. J., 570*
- Bruenn, Howard G., Williams, N. E., Carr, H. A., and Levy, R. L., 252
- Burch, G. E., Neumann, C., and Cohn, A. E., 276
- Burchell, Howard B., and Visseher, M. B., 794
- Burton, A. C., Jeffers, W. A., Montgomery, H., 572*
- Burwell, C. Sidney, and Ayer, G. D., 267

C

- Calcium, action of, on human electrocardiogram, 367
- Cameron, D. E., and Rosen, S. R., 427*
- Campbell, H. E., 715*
- Capillaries, studies of, in Raynaud's disease, 573*
- Carbon dioxide, action, physiologic, of oxygen and, as shown by blood gas and electrocardiographic studies, 13
- Cardiac classics, collection of classic works on heart and circulation, with comprehensive bibliographic accounts of authors, 578 (B. rev.)
- Cardiovascular system, consideration of effect of oxygen lack on, from viewpoint of aviation, 839*
- control, hypothalamic, of, analysis of, 562*
- disease of, diagnosis and treatment of, 433 (B. rev.)
- estimation of cardiac output from blood pressure and pulse wave velocity measurement on subjects with. I. Cardiovascular disease other than aortic regurgitation, 737
- II. Aortic regurgitation, 749
- pathology of, experimental studies of. II. Pathologic lesions in organs of cats, guinea pigs, and frogs produced by digitalis poisoning, 430*
- Carotid sinus syndrome, surgery in, 428*
- Carr, F. B., 570*
- Carr, Henry A., Williams, N. E., Bruenn, H. G., and Levy, R. L., 252
- Castleman, Benjamin, Ruffin, M. deG., and White, P. D., 458
- , Talbott, J. H., Coombs, F. S., Chamberlain, F. L., Consolazio, W. V., and White, P. D., 734
- Cattell, M., and Gold, H., 848*
- Chagas' disease (*see* trypanosomiasis)

- Chamberlain, Francis L., Talbott, J. H., Coombs, F. S., Castleman, B., Consolazio, W. V., and White, P. D., 754
- Childbearing age, heart in pregnancy and, 431 (B. rev.)
- Childhood, rheumatic infection in, influence of type of onset and calendar year of onset, 439
- Children, character of congestive failure in, with active rheumatic fever, 283*
- incidence of heart disease in, with congenital syphilis, 844*
- rheumatic, epidemic of influenza B occurring in group of, concurrent with outbreak of streptococcal pharyngitis, 282*
- observation on effect of streptococcal upper respiratory infections in, 282*
- school, incidence of rheumatic and congenital heart disease among, of Louisville, Ky., 112
- Ch'in, K. Y., and Huang, C. H., 690
- Chorea, Sydenham's, treatment of, by fever and vitamin B therapy, 426*
- Christian, H. A., 132*
- Circulation, coronary, action, physiologic, of oxygen and carbon dioxide on, as shown by blood gas and electrocardiogram studies, 13
- capacity of, in cardiac hypertrophy, 565*
- insufficiency of, further observations on effect of certain xanthine compounds in cases of, as indicated by response to induced anoxemia, 252
- observations on morphology and functions of some of components of, 564*
- influence of gas-mask breathing on, of men, 427*
- of thyroid hormone on heart and, 577 (B. rev.)
- observations, experimental, on effect of hydrostatic forces on, 839
- peripheral, failure of, in diabetic acidosis and its relations to treatment, 564*
- failure of mechanisms of, 714*
- problems of, 575*
- renal, capacity of, in hypertension, 565*
- resistance, peripheral, of, evidence for general distribution of, in coarctation of aorta, 567*
- time, arm to lung, of, comparative value of ether and paraldehyde as agents for measurements of, in fifty patients with and fifty patients without heart failure, 284*
- venous, in lower extremities during pregnancy, 427*
- Clark, C. J., and Browning, J. S., 570*
- Clarke, Norman E., 367
- Clarke, William O., and Hallock, P., 410
- Claudication, intermittent, as result of arterial spasm induced by walking, 719
- Clawson, B. J., 607
- Coarctation of aorta, evidence for general distribution of peripheral resistance in, 567*
- Cohen, Louis, Gray, I., Nash, P. T., and Fink, H., 425*
- , Lalich, J., and Walker, G., 105
- Cohn, A. E., Neumann, C., and Burch, G. E., 276*
- Cohn, C., Schecter, A. E., and Wiesel, B. H., 564*
- Collapse, factor of, in measurement of venous pressure, flow of fluid through collapsible tubes, 562*
- Complex, QRS, duration of, measurement of, errors in, and P-R (P-Q) interval in electrocardiogram, 321
- prolongation of, further observations on mechanisms of production of short P-R interval in association with, 450
- significance of low voltage of, in precordial leads, 195
- R, formation of, of electrocardiogram, 567*
- ventricular, variable, in heart block, and their relation to bilateral bundle branch block, 280*
- Consolazio, W. V., Talbott, J. H., Coombs, F. S., Castleman, B., Chamberlain, F. L., and White, P. D., 754*
- Cooke, W. T., and White, P. D., 425*
- Coombs, Frederick S., Talbott, J. H., Castleman, B., Chamberlain, F. L., Consolazio, W. V., and White, P. D., 754*
- Cor pulmonale (*see* heart, hypertrophy)
- Corbit, J. D., Jr., 283*
- , Fouts, P. J., and Page, I. H., 714*
- Corcoran, A. C., and Page, I. H., 132*, 571*
- , Smith, H. W., and Page, I. H., 571*
- Correspondence, 581
- Corrigendum, 275
- Cos, A. J., Jr., and Dock, W., 565*
- Cossio, P., Berconsky, I., and Gamba, R., 281*
- Crouch, J. H., 574*
- Croxatto, R., Garretton-Silva, A., Fuenzalida, O., and Viveros, R., 284*
- Cushing, Edward H., and Liebow, I. M., 125
- Cyclopropane, effect of, on blood pressure, stroke volume, and heart size of dog, 563*

D

- Da Costa's syndrome (*see* effort syndrome)
- Dally, J. F. H., 564*

- Davis, David, Iglauer, A., and Altschule, M. D., 47
- Death, physiologic, instantaneous, 278*
sudden, symposium on, 277*, 278*
syphilitic aortitis as cause of, 277*
- Denenholz, E., and Rambar, A. C., 426*
- Depropanex (*see* pancreas, extract of)
- Deutsch, F., Ehrentheil, O., and Peirson, O., 573*
- Diabetes, acidosis of, treatment of, peripheral circulatory failure in, and its relation to, 564*
- Digitalis and normal work electrocardiogram, 683
glucosides, purified, of, studies on. III. Relationship between therapeutic and toxic potency, 848*
poisoning by, pathologic lesions in organs of cats, guinea pigs, and frogs produced by, 430*
study, electrocardiographic, quantitative, of, 230
use of, to prevent exaggerated acceleration of heart during physical exercise in patients with auricular fibrillation, 430*
- Digoxin, effect of, on cold blooded heart and its bearing on mechanism of digitalis action, 847*
- Diodrast, removal of, from blood by dog's explanted kidney, 571*
- Diphtheria, myocardial necrosis in, 690
- Diuretics, mercurial, comparison of, used in heart failure, 428*
- Dock, W., 565*
- , and Cos, A. J., Jr., 565*
- Dressler, M., and Moskowitz, S. N., 566*
- Druckemiller, William H., Geiger, A. J., and Blaney, L. F., 230
- Drugs, action of, further observations on, on caliber of coronary vessels, 846*
- Dungern, M., 841*
- Duryee, A. Wilbur, Schwartz, M. S., Fisher, M. M., and Wright, I. S., 122
- Dwyer, C. K., Wedd, A. M., and Blair, H. A., 847*

E

- Eckman, Morris, Barach, A. L., Steiner, A., and Molomut, N., 13
- Eckstein, R. W., Roberts, J. T., Gregg, D. E., and Wearn, J. T., 276*
- Ectasia, senile, aneurysms, arteriosclerotic, and, of thoracic aorta, 458
- Edema, treatment of, and angina pectoris, prolonged use of enteric-coated tablets of theobromine sodium acetate in, 847*
- Effort syndrome, 286*
- Ehrentheil, O., Deutsch, F., and Peirson, O., 573*
- Electrocardiogram, action, physiologic, of oxygen and carbon dioxide on coronary circulation as shown by blood gas and, 13
- Electrocardiogram—Cont'd
alterations in, duration of isometric contraction, ejection time, systole, and Q-T interval, 841*
aspects, clinical, of, 287 (B. rev.)
changes following intravenous administration of magnesium sulfate. III. Combined effect with digitalis, 429*
in occurrence of, in angina pectoris similar in magnitude and in kind to those produced by myocardial infarction, 64
in rhythm of heart during resection of pericardium in chronic constrictive pericarditis, 169
of chest-leads of, due to damage to heart's surface, 425*
characteristic, in left ventricular strain with and without axis deviation, 279*
comparison of Leads IV R and IV F, 125
distribution of surface potential in chest intraventricular block, 778
duration of Q-T interval in absolute arrhythmia, 841*
in cases of massive pericardial effusion, 35
errors in, measurement of P-R (P-Q) interval and QRS duration in, 321
esophageal, normal and abnormal, with particular reference to myocardial infarction, 469
formation of R complex of, 567*
human action of calcium in, 367
in acute emetine intoxication, 715*
in experimental Chagas' disease, 567*
in induced fever, 804
nature of Leads I and II, 567
normal, 625
pattern of, effect of diffuse pericarditis on, of recent myocardial infarction, 86
significance of low voltage of QRS complex in precordial leads as compared with limb leads, 195
S-T depression, as sign of anaerobic cardiac metabolism, 841*
studies by, analysis of initiation of fibrillation, 713*
variations of, frequency of, in normal unanesthetized dogs, 105
ventricular, physiological variations in duration of, 841*
work, normal, digitalis and, 683
- Electrocardiography, fetal, 390
and stethography, 840*
for practicing physician, 433 (B. rev.)
- Elkin, D. C., 137*
- Embolism, fat, clinical and experimental study, 424*
- Emetine, intoxication, acute, by electrocardiogram in, 715*

- Endocarditis, bacterial, acute, ruptured aortic valve with mycotic aneurysm due to, 426*
 subacute, treatment of, 286*
 subacute *Streptococcus viridans*, earlier diagnosis of, 132*
- Estrogen, action, dermovascular, of, 575*
- Ether, value, comparative, of, and paraldehyde as agents for measurements of arm to lung circulation time in fifty patients with and fifty without heart failure, 284*
- Evans, W., and Paxon, T., 428*
- Exercise, peripheral vascular response to, in hyperthyroid state, 566*
 physical, use of digitalis to prevent exaggerated acceleration of heart during, in patients with auricular fibrillation, 430*
 venous pressure responses to, 360
- Eyster, J. A. E., and Meek, W. J., 839*
- F
- Farmer, L., Wechsler, H. F., and Urban, J. A., 280*
- Fatherree, T. J., and Hurst, C., 180
- Feil, Harold, and Beck, C. S., 846*
- , and Liebow, I. M., 683
- Feldt, R. H., and Wenstrand, D. E. W., 424*
- Ferris, Eugene B., Jr., Abramson, D. I., and Katzenstein, K. H., 329
- Fetus, electrocardiogram in, 390
- Fever, induced, electrocardiogram in, 804
- Fibrillation, auricular, following injection of acetyl- β -methylcholine chloride (mecholyl) during attack of paroxysmal auricular tachycardia or flutter, 425*
 in normal intact animals after intravenous injection of mecholyl, 47
 use of digitalis to prevent exaggerated acceleration of heart during physical exercise in patients with, 430*
 variable interval between electric and acoustic phenomena in, 245
 duration of Q-T interval in, 841*
 initiation of, analysis of, by electrographic studies, 713*
 ventricular, ineffectiveness of vagal stimulation on, in dogs, 276*
- Fierst, S. M., and Abramson, D. I., 566*
- Fink, H., Cohen, L., Gray, I., and Nash, P. I., 425*
- Fishberg, Arthur M., 139
- Fisher, Martin M., Schwartz, M. S., Wright, I. S., and Duryee, A. W., 122
- Fistula, arteriovenous, clinical and experimental observations on, 135*
- Flaxman, N., 279*
- Foote, Stephen A., White, P. D., and Leach, C. E., 321
- Foreign body, bullet, in heart for twenty-three years, 575*
 needle, hollow, passage of, into venous blood stream to heart through cardiac wall and into thorax, 835
 -gas method, estimation by, of net cardiac output in conditions where there is recirculation through lungs, 561*
- Fouts, P. J., Corcoran, A. C., and Page, I. H., 714*
- Freedberg, A. Stone, Riseman, J. E. F., and Spiegl, E. D., 494, 519
- Frey, J., 839
- Friedman, B., Jarman, J., and Klempner, P., 572*
- Friedman, M., Sugarman, H., and Selzer, A., 844*
- Fuenzalida, O., Garreton-Silva, A., Croxatto, R., and Viveros, R., 284*
- Fujiwara, T. F., Karsner, H. T., and Simon, M. A., 423*
- G
- Gage, M., and Ochsner, A., 137*
- Galdston, M., Govons, S., Wortis, S. B., Steele, J. M., and Taylor, H. K., 572*
- Gamba, R., Cossio, P., and Bereonsky, I., 281*
- Gangrene, ischemic, prevention of, following surgical operations upon major peripheral arteries by chemical section of cervicodorsal and lumbar sympathetics, 137*
- Garreton-Silva, A., Croxatto, R., Fuenzalida, O., and Viveros, R., 284*
- Garvin, Curtis F., and Scott, R. W., 56
- Geiger, Arthur J., Blaney, L. F., and Druckemiller, W. H., 230
- Gilligan, D. Rourke, Blumgart, H. L., and Schlesinger, M. J., 374
- Glaser, S. T., and Lesser, A., 428*
- Glomerulonephritis, acute, mode of action of magnesium sulphate in reducing hypertension of, 576*
- Glomus tumors, clinical picture and physiology, 574*
 multiple, four in one finger tip, 574*
- Gold, H., and Cattell, M., 848*
- , Modell, W., and Rothendler, H. H., 430*
- Gorenberg, H., and McCleary, J., 842*
- Gouley, Benjamin A., 208
- Govons, S., Galdston, M., Wortis, S. B., Steele, J. M., and Taylor, H. K., 572*
- Gray, Howard K., and Skinner, I. C., 428*
- Gray, I., Cohen, L., Nash, P. I., and Fink, H., 425*
- Graybiel, A., 839*
- , and White, P. D., 561*

Greenfield, Irving, 707
 Gregg, D. E., Eckstein, R. W., Roberts, J. T., and Wearn, J. T., 276*
 Gross, F., and Matthes, K., 840*
 Growth, alterations in heart accompanying, and hypertrophy, 564*

H

Hahn, P., 568*
 Hallock, Phillip, and Clarke, W. O., 410
 Hamburger, Walter W., in memoriam, 850
 Hamilton, Burton E., and Thomson, K., 431
 Hannesson, H., 843*
 Harris, A. S., Moe, G. K., and Wiggers, C. J., 713*
 Heart, acceleration, exaggerated, use of digitalis to prevent, during physical exercise in patients with auricular fibrillation, 430*
 alterations in, accompanying growth and hypertrophy, 564*
 anoxemia of, S-T depression as sign of, 841*
 arrhythmia, absolute, of (*see* fibrillation, auricular)
 beat, idioventricular, of, comparison of vulnerable periods and fibrillation thresholds of, 277*
 block, auriculo-ventricular, complete, intermittent, three observations on, 425*
 with Stokes-Adams' syndrome in patient with syphilitic heart disease and diffuse myocarditis, 569*
 bundle branch, bilateral, variable ventricular complexes in heart block and their relations to, 280*
 pulmonary stenosis with, 280*
 intraventricular, distribution of surface potential in chest, 778
 ventricular complexes, variable, in, and their relation to bilateral bundle branch block, 280*
 bullet in, for twenty-three years, 575*
 compression, chronic, of, effect of, on size of heart muscle fibers, 314
 contraction, fractionate, sequence of, at different surface regions on right auricle and ventricles of dog's heart, 839*
 disease of, anesthesia in relation to, 846*
 choice of anesthesia in operative patients with, 285*
 congenital, incidence of rheumatic and, among school children of Louisville, Ky., 112
 geographical distribution of, incidence of rheumatic and congenital heart disease among school children of Louisville, Ky., 112
 in pregnancy, 570*

Heart, disease of—Cont'd

incidence of, in children with congenital syphilis, 844*
 of types of, among 30,265 autopsies, with special reference to age and sex, 607
 physiology, examination and functional pathology of heart (vol. I), 437 (B. rev.)
 review of significant contributions made during 1940, 561*
 rheumatic, in Philadelphia Hospitals. IV. Influence of season and certain meteorological conditions, 133*
 V. Distribution by locality of rheumatic conditions in Philadelphia, 134*
 in pregnancy, 842*
 incidence of, and congenital heart disease among school children in Louisville, Ky., 112
 influence of tonsillectomy on progress of, 133*
 synopsis of, and arteries, 716 (B. rev.)
 syphilitic, of, auriculo-ventricular heart block with Stokes-Adams' syndrome in patient with, and diffuse myocarditis, 569*
 factor of, in "pressor" effects of renin and angiotonin, 423*
 failure of, comparative value of ether and paraldehyde as agents for measurement of arm to lung circulation time in fifty patients with and fifty patients without, 284*
 comparison of, mercurial diuretics used in, 428*
 congestive, character of, in children with active rheumatic fever, 283*
 of, studies on. I. Importance of restriction of salt as compared with water, 141
 hydrothorax in, 285*
 myocardial degeneration with hypertrophy and, of unknown cause, 811
 production and study of, in thiamin-deficient dogs, 154
 filling and rate of, effect of respiration on, 712*
 hypertrophy of, alterations in heart accompanying growth and, 564*
 capacity of coronary bed in, 565*
 myocardial degeneration, and failure of unknown cause, 811
 observations in fifty autopsy cases, 56
 in pregnancy and childbearing age, 431 (B. rev.)
 influence of thyroid hormone on, and circulation, 577 (B. rev.)
 insufficiency of, 577 (B. rev.)

Heart—Cont'd

- mammalian, beating, changes in form of, as demonstrated by high-speed photography, 794
- surviving, energetics of, effect of varying resistance-load and input-load on, 712*
- murmur, Austin Flint, of, aortic valvular lesions associated with, 208
- muscle of (*see* myocardium)
- output of, estimation of, from blood pressure and pulse wave velocity measurements on subject with cardiovascular disease. I. Cardiovascular disease other than aortic regurgitation, 737
- II. Aortic regurgitation, 749
- output of, net (systemic) of, estimation by foreign-gas method of, in conditions where there is re-circulation through lungs, 561*
- rhythm of, changes in, during resection of pericardium in chronic constrictive pericarditis as recorded electrocardiographically, 169
 - gallop, systolic, of, 726
 - nodal, atrioventricular, of, 279*
- rupture, spontaneous, of, 569*
 - reflections on mechanism of, 568*
- sarcoma, primary, of, 556
- size of, effect of cyclopropane on blood pressure, stroke volume and, of dog, 563*
- stroke volume of, effect of cyclopropane on blood pressure, and heart size of dog, 563*
- surface of, abrasion of, effect of, upon intercoronary communications, 529
 - damage of, changes of chest-leads of electrocardiogram due to, 425*
- tuberculosis of pericardium and, 843*
 - your, 716 (B. rev.)
- Heat, body, conservation and dissipation of, autonomic mechanism of.
 - I. Effect of heating body, evidence for existence of capillary dilator nerves in anterior roots, 289
- Hedley, O. F., 133,* 134*
- Heinbecker, Peter, 138*
- Herrington, L. P., and Nelbach, J. H., 661
- Herrmann, George R., 716
- Herrmann, Louis G., and Neel, W., 702
- Hertzman, A. B., 574*
- Hildebrandt, F., 849*
- Hill, W. H. P., and Andrus, E. C., 423*
- Hines, E. A., Jr., and Lander, H. H., 135*
- Hinohara, Shigeaki, 726
- Hochrein, Max, 437
- von Hofer, H., 427*
- Hoff, H. E., Nahum, L. H., and Kaufman, W., 567*
- Holman, Emile, 135*
- Holt, J. P., 562*
- Horneff, J. A., and Sappington, S. W., 573*
- Horswell, Richard G., 116
- Huang, C. H., and Ch'in, K. Y., 690
- Hubbard, J. P., 282*
- Hueper, W. C., and Ichniowski, C. T., 430*
- Hunter, W. C., Sneed, V. D., Robertson, T. D., and Snyder, G. A. C., 574*
- Hurst, Cecil, and Fatherree, T. J., 180
- Hussey, H. H., and Katz, S., 284*
- , and Veal, J. R., 427*
- Hydrothorax in heart failure, 285*
- Hyndman, Olan R., and Wolkin, J., 289
- Hyperemia, reaction, observations on, on various portions of extremities, 329
- Hypertension and nephritis, 139 (B. rev.)
 - and pressor activity of heated extracts of human kidneys, 426*
 - arterial, correlation of clinical and experimental observations, 132*
 - experimental investigation of pressor substances with blood of patients with, 284*
 - pulmonary, experimental, relation of, to arteriosclerosis, 423*
 - association of, with organic renal disease, 570*
 - capacity of renal vascular bed in, 565*
 - essential, role for surgeon in problem of, 138*
 - studies on. II. Association of hypertension with organic renal disease, 570*
 - experimental and clinical aspects of, 571*
 - effect of pregnancy upon, in rabbit, 283*
 - production of, relationship of renal blood pressure and blood flow to, 844*
 - factors contributing to development of, in patients suffering from renal disease, 135*
 - kidney, unilateral, with partial occlusion of renal artery associated with, 284*
 - of acute glomerulonephritis, mode of action of magnesium sulphate in reducing, 576*
 - sustained, following experimental unilateral renal injuries, effects of nephrectomy, 572*
- Hyperthyroidism, peripheral vascular response to exercise in, 566*
- Hypotension, orthostatic, types of, and their treatment, 572*

I

Ichniowski, C. T., and Hueper, W. C., 430*

- Iglauer, Arnold, and Altschule, M. D., 430*
 —, Davis, D., and Altschule, M. D., 47
 Infancy, medical coronary sclerosis in, 132*
 Infant, newborn, rheumatic fever in, 426*
 young, paroxysmal tachycardia and its treatment in, 282*
 Influenza B, epidemic of, occurring in group of rheumatic children concurrent with outbreak of streptococcal pharyngitis, 282*
 Input-load, effect of varying resistance-load and, on energetics of surviving mammalian heart, 712*
 Insulin, allergy to, case of, simulating coronary occlusion, 280*
 Isard, H. J., and Baer, S., 713*

J

- Jarman, J., Friedman, B., and Klemperer, P., 572*
 Jason, R. S., 569*
 Jean, Nicholas Corvisart, life and times of, 564*
 Jeffers, W. A., Montgomery, H., and Burton, A. C., 572*
 Jochim, K., Katz, L. N., Lindner, E., and Landowne, M., 712*
 Johnson, C. A., 284*
 Johnston, Franklin D., and Wilson, F. N., 64
 Jones, Benjamin C., Jr., and Weir, D. R., 556

K

- Kaplan, L. G., and Katz, L. N., 279*
 Karsner, H. T., Simon, M. A., and Fujiwara, T. F., 423*
 Katz, L. N., Bohning, A., and Langendorf, R., 778
 —, Jochim, K., Lindner, E., and Landowne, M., 712*
 —, and Kaplan, L. G., 279*
 —, and Lindner, E., 846*
 Katz, S., and Hussey, H. H., 284*
 Katzenstein, Kurt H., Abramson, D. I., and Ferris, E. B., Jr., 329
 Kaufman, W., Hoff, H. E., and Nahum, L. H., 567*
 Kershbaum, Alfred, and Bellet, S., 195
 Keys, A., 561*
 Keys, Thomas E., and Willius, F. A., 578
 Kidney, disease of, factors contributing to development of hypertension in patients suffering from, 135*
 organic, association of hypertension with, 570*
 formulae for afferent and efferent arteriolar resistance in, application to effects of spinal anesthesia, 571*
 injury, experimental, unilateral, of sustained hypertension following effect of nephrectomy, 572*

- Kidney, injury—Cont'd
 explanted, dog's, removal of diodrast from blood by, 571*
 unilateral, with partial occlusion of renal artery associated with hypertension, 284*
 Kienle, Franz, 436
 Kisch, B., 425*
 Kissane, R. W., and Koons, R. A., 844*
 Klemperer, P., Friedman, B., and Jarman, J., 572*
 —, Pollack, A. D., and Baehr, G., 842*
 Knies, Phillip T., 804
 Koons, R. A., and Kissane, R. W., 844*
 Kruger, Erich, McGovern, T., and Wright, I. S., 583
 Krumwiede, E., and Kuttner, A. G., 282*
 Kuttner, A. G., and Krumwiede, E., 282*
 —, Reyersbach, G., and Lenert, T. F., 282*

L

- Lalicch, Joseph, Cohen, L., and Walker, G., 105
 Lamport, H., 571*
 Lander, H. H., and Hines, E. A., Jr., 135*
 Landis, E. M., 426*
 Landowne, M., Katz, L. N., Jochim, K., and Lindner, E., 712*
 Langendorf, R., 86
 —, Bohning, A., and Katz, L. N., 778
 Laplace, L. B., Bazett, H. C., and Scott, J. C., 737, 749
 Larrabee, M. G., Pitts, R. F., and Bronk, D. W., 562*
 Larsen, Kaj, and Skúlason, Th., 625, 645
 Laufer, S. T., 842*
 Leach, C. Edward, White, P. D., and Foote, S. A., 321
 Leads, chest, changes of, of electrocardiogram due to damage of heart's surface, 425*
 IV R and IV F, comparison of, 125
 precordial, significance of low voltage of QRS complex in, comparison with limb leads, 195
 Leaman, William G., 579
 Leary, T., 277,* 845*
 Leary, Walter V., and Allen, E. V., 719
 Lenert, T. F., Reyersbach, G., and Kuttner, A. G., 282*
 LeRoy, G. V., 576*
 Lesser, A., and Glaser, S. T., 428
 Levine, Samuel A., and Beeson, P. B., 401
 Levy, Robert L., Williams, N. E., Carr, H. A., and Bruenn, H. G., 252
 Lichtman, S. S., and Bierman, W., 286*
 Liebow, A. A., and McFarland, W., 568*
 Liebow, Irving M., and Cushing, E. H., 125
 —, and Feil, H., 683
 Lindner, E., and Katz, L. N., 846*
 —, —, Jochim, K., and Landowne, M., 712*
 Linenthal, Harry, and Riseman, J. E. F., 219, 847*

- Lladó, Cristián Cortés, 577
 Louisville, Ky., incidence of rheumatic and congenital heart disease among school children of, 112
 Lovibond, J. L., and Bedford, D. E., 285*
 Lucia, S. P., Aggeler, P. M., and Thompson, J. H., 825
 Luisada, Aldo, 245
 Lungs, ossification, nodular of, pulmonary stenosis and, 281*
 Lupus, erythematosus, disseminated, pathology of, 842*

M

- Magnesium sulfate, electrocardiographic changes following intravenous administration of. III. Combined effect with digitalis, 429*
 mode of action in reducing hypertension of acute glomerulonephritis, 576*
 Mann, Hubert, and Bernstein, P., 390
 Matthes, K., and Gross, F., 840*
 McCleary, J., and Gorenberg, H., 842*
 McDowall, R. J. S., 575*
 McFarland, W., and Liebow, A. A., 568*
 McGovern, Teresa, Wright, I. S., and Kruger, E., 583
 Mecholyl (*see* acetyl- β -methylcholine)
 Meek, W. J., and Eyster, J. A. E., 839*
 Meiks, L. T., 133*
 Metabolism, disorders, various, of, correlation of velocity of blood flow and basal metabolic rate in, 713*
 rate, basal, of, correlation of velocity of blood flow and, in various metabolic disorders, 713*
 Miller, J. R., and Van Dellen, T. R., 429*
 Modell, W., Gold, H., and Rothendler, H. H., 430*
 Moe, G. K., Harris, A. S., and Wiggers, C. S., 713*
 —, Wégria, R., and Wiggers, C. J., 277*
 Molomut, Norman, Barach, A. L., Steiner, A., and Eckman, M., 13
 Montgomery, H., Jeffers, W. A., and Burton, A. C., 572*
 Montgomery, L. C., 427*
 Moritz, A. R., 278*
 Moskowitz, S. N., and Dressler, M., 566*
 Mulholland, John H., and Rovenstine, E. A., 428*
 Myocarditis, diffuse, auriculo-ventricular heart block with Stokes-Adams' syndrome in patient with syphilitic heart disease and, 569
 Myocardium, contusion of, fatal case of, 280*
 degeneration of, with hypertrophy and failure of unknown cause, 811
 disease of, observations on production of, with acetylcholine, 116

Myocardium—Cont'd

- fibers of, size of, effect of chronic cardiac compression on, 314
 infarction of, electrocardiogram, normal and abnormal esophageal with particular reference to, 469
 occurrence of electrocardiographic changes in angina pectoris, similar in magnitude and in kind to those produced by, 64
 production of, experimental studies on effect of temporary occlusion of coronary arteries, 374
 recent, effect of diffuse pericarditis on electrocardiographic pattern of, 86
 subacute, of, or necrosis, 842*
 necrosis of, in diphtheria, 690

N

- Nahum, L. H., Hoff, H. E., and Kaufman, W., 567*
 Nash, P. I., Cohen, L., Gray, I., and Fink, H., 425*
 Nature therapy studies of treatment of heart disease, 436 (B. rev.)
 Neel, William, and Herrmann, L. G., 702
 Nelbach, Jean Hume, and Herrington, L. P., 661
 Nephritis, hypertension and, 139 (B. rev.)
 nephrotoxic, observations on clinical and functional course of, in dogs, 714*
 Nerves, capillary, dilator, evidence for existence of, in anterior roots, 289
 vagus, stimulation of, ineffectiveness of, on ventricular fibrillation in dogs, 276*
 Neumann, C., Cohn, A. E., and Burch, G. E., 276*
 Nomenclature, diseases and abnormalities of blood and lymph vessels of extremities, 549
 Nyboer, Jan, 469

O

- Obituaries, 850, 852
 Occlusion, experimental, sympathectomy and, of coronary artery, 545
 Ochsner, A., and Gage, M., 137*
 Octyl nitrite, in treatment of angina pectoris, 519
 Old age, reactivity of intracranial vessels in, 427*
 Osborn, G. R., and Barber, H., 280*
 Oxygen, action, physiologic, of, and carbon dioxide, on coronary circulation as shown by blood gas and electrocardiographic studies, 13
 lack of, effects of, consideration of, on cardiovascular system from viewpoint of aviation, 839*

P

- Page, I. H., and Corcoran, A. C., 132,*
571*
- , —, and Smith, H. W., 571*
- , Fouts, P. S., and Corcoran, A. C.,
714*
- Pain, disabling, syndrome of, of shoulder
and hand, complicating coronary
occlusion, 1
studies on, observations on pain due
to local cooling and on factors
involved in "cold pressor"
effect, 566*
- Pancreas extract, deproteinated, effect
of intravenous administration
in rabbits, 122
- Paraldehyde, value, comparative, of ether
and, as agents for measurement
of arm to lung circulation in
fifty patients with and fifty
patients without heart failure,
284*
- Pardee, Harold E. B., 287*
- Paredrine (*see* p-hydroxy- α -methylphenyl-
ethylamine hydrobromide)
- Parker, F. P., and Blackford, L. M.,
280*
- Patient, cardiac, management of, 579
(B. rev.)
- Patras, Mary C., and Boyd, T. E., 561*
- Paxon, T., and Evans, W., 428*
- Pearse, H. E., 137*
- Peirson, O., Deutsch, F., and Ehren-
theil, 573*
- Pericarditis, constrictive, chronic,
changes in rhythm of heart
during resection of pericar-
dium as recorded electrocar-
diographically, 169
pleuritis and, 267
diffuse, effect of, on electrocar-
diographic pattern of recent myo-
cardial infarction, 86
leucemic, 417
- Pericardium, effusion, massive, in dura-
tion of electrical systole (Q-T
interval) in cases of, 35
resection, changes in rhythm of heart
during, in chronic constrictive
pericarditis as recorded elec-
trocardiographically, 169
tuberculosis of, and heart, 843*
- p-hydroxy- α -methylphenylethylamine hy-
drobromide, effect of arterial
and venous constriction in-
duced by, on lung capacity and
its subdivisions, 430*
- Peripheral vascular system, disease of,
pernio, 583
- Pernio, vascular disease, 583
- Philadelphia, Hospital of, rheumatic dis-
ease in, 133,* 134*
- Photography, high-speed, changes in
form of beating mammalian
heart as demonstrated by,
794
- Pitts, R. F., Larrabee, M. G., and
Bronk, D. W., 562*

- Pleuritis, constrictive, and pericarditis,
267
- Plewes, B., 574*
- Pollack, A. D., Klemperer, P., and
Baehr, G., 842*
- Porter, Reno R., Swank, R. L., and
Yeomans, A., 154
- Posture, change of, alternations of T
waves caused by, 279*
- P-R interval, measurement of, errors in,
and QRS duration in electro-
cardiogram, 321
short, further observations on mech-
anism of production of, in
association with prolongation
of QRS complex, 450
- Prado, A. De A., 569*
- Pregnancy, effect of, on experimental
hypertension in, in rabbit,
283*
heart disease in, 570*
heart disease, rheumatic, in, 842
heart in, and childbearing age, 431
(B. rev.)
paroxysmal auricular tachycardia com-
plicating, 570*
venous circulation in lower extremities
during, 427*
- Pressor activity, hypertension and, of
heated extracts of human
kidneys, 426*
substance, investigation, experimental,
with blood of patients with
arterial hypertension, 284*
- Pulse wave, velocity of, estimation of
cardiac output from blood
pressure measurements of, on
subjects with cardiovascular
disease. I. Cardiovascular
disease other than aortic re-
gurgitation, 737
II. Aortic regurgitation, 749

Q

- Q-T interval, duration of, in absolute
arrhythmia, 841*
in cases of massive pericardial ef-
fusion, 35
- Quinine dihydrochloride, treatment of
paroxysmal ventricular tachy-
cardia with, 219

R

- Rambar, A. C., and Denenholz, E., 426*
- Rapoport, M., and Rubin, M. I., 576*
- Rasmussen, Hakon, 577
- Raynaud's disease, capillary studies in,
573*
symptoms of, study of clinical mani-
festations and results of
treatment of twenty-two pa-
tients with, 284*
- Reid, L. C., 846*
- Reisinger, John A., and Blumenthal, B.,
811
- Renin, effects, "pressor," of, and angio-
tonin, cardiac factor in, 423*

- Resistance-load, effect of varying, and input-load on energetics of surviving mammalian heart, 712*
- Respiration, effect of, on filling and rate of heart, 712*
- phases of, variations in filling and output of ventricles with, 561
- Reyersbach, G., Lenert, T. F., and Kuttner, A. G., 282*
- Reynolds, S. R. M., 575*
- Rheumatic fever, active, character of congestive failure in children with, 283*
- blood picture in, 342
- children with, epidemic of influenza B occurring in group of, concurrent with outbreak of streptococcal pharyngitis, 282*
- in childhood, influence of type of onset and calendar year of onset, 439
- in newborn infant, 426*
- observations on effect of streptococcal upper respiratory infections on, 282*
- Richter, I. M., and Brown, C. E., 132*
- Riggs, T. F., and Satterthwaite, R. W., 284*
- Riseman, Joseph E. F., Freedberg, A. S., and Spiegl, E. D., 494, 519
- , and Linenthal, H., 219, 847*
- Roberts, Joseph T., and Beck, C. S., 314
- , Eckstein, R. W., Gregg, D. E., and Wearn, J. T., 276*
- Robertson, T. D., Hunter, W. C., Sneed, V. D., and Snyder, G. A. C., 574*
- Rosen, S. R., and Cameron, D. E., 427*
- Rovenstein, E. A., and Mulholland, J. H., 428*
- Rubin, M. I., and Rapoport, M., 576*
- Ruffin, Marshall deG., Castleman, B., and White, P. D., 458
- Rupture, spontaneous, of heart, 569*
- reflections on mechanism of, 568*
- S
- Salt, restriction of, importance of, as compared with water, in congestive heart failure, 141
- Sappington, S. W., and Horneff, J. A., 573*
- Sarcoma, primary, of heart, 556
- Satterthwaite, R. W., and Riggs, T. F., 284*
- Sauer, P. K., 285*
- Scheeter, A. E., Wiesel, B. H., and Cohn, C., 564*
- Scherf, D., and Boyd, L. S., 715*
- , Brace, D. E., and Spire, L. J., 563*
- , and Weissberg, J., 279*
- Schildt, Paul, Stanton, Eugene J., and Beck, C. S., 529
- Schleicher, I., 845*
- Schlesinger, Monroe J., Blumgart, H. L., and Gilligan, D. R., 374
- , —, and Zoll, P. M., 568*
- Schroeder, Harry A., 141
- , and Steele, J. M., 570*
- Schwartz, M. Stephen, Fisher, M. M., Wright, I. S., and Duryee, A. W., 122
- Scott, J. C., Bazett, H. C., and Laplace, L. B., 737, 749
- Scott, Roy W., and Garvin, C. F., 56
- Scuderi, C. S., 423*
- Selzer, A., Friedman, M., and Sugarman, H., 844*
- Shapiro, Shepard, 835
- Simbury, E. J., 569*
- Simon, M. A., Karsner, H. T., and Fujiwara, T. F., 423*
- Skin temperature, cooling, local, of, observations on pain due to, and on factors involved in "cold pressor" effect, 566*
- Skinner, I. C., and Gray, H. K., 428
- Skúlason, Th., and Larsen, Kaj, 625, 645
- Smith, H. W., Corcoran, A. C., and Page, I. H., 571*
- Sneed, V. D., Hunter, W. C., Robertson, T. D., and Snyder, G. A. C., 574*
- Snyder, G. A. C., Hunter, W. C., Sneed, V. D., and Robertson, T. D., 574*
- Spiegl, Erwin D., Freedberg, A. S., and Riseman, J. E. F., 494, 519
- Spinal cord, ischemia of, in dissecting aortic aneurysm, 305
- Spire, L. J., Brace, D. E., and Scherf, D., 563*
- Spitzer's theory, "corrected transposition" and persistent rudimentary "right aorta" as evidence in support of, 568*
- Sprague, H. B., and Walsh, B. J., 283*
- Stanton, Eugene J., Schildt, P., and Beck, C. S., 529
- Starr, L., 712*
- Statistics, vital tool in clinical medicine, 715*
- Steele, J. M., 567*
- , Galdston, M., Govons, S., Wortis, S. B., and Taylor, H. K., 572*
- , and Schroeder, H. A., 570*
- Stein, Joseph M., 716
- Steiner, Alfred, Barach, A. L., Eckman, M., and Molomut, N., 13
- Stethography, fetal electrocardiography and, 840*
- Stewart, Harold, J., and Bailey, R. L., Jr., 169
- Stokes-Adams' syndrome, auriculo-ventricular heart block with, in patient with syphilitic heart disease and diffuse myocarditis, 369*
- Stone, S., 426*
- Streptococcus pharyngitis, epidemic of influenza B occurring in group of rheumatic children concurrent with outbreak of, 282*

- Streptococcus—Cont'd
upper respiratory infections with observations on effect of, on rheumatic children, 282*
- Strombeck, J. P., 423*
- Strophanthin, action of, on blood vessels, 849*
- Stroud, W. D., 433
- , and Wagner, J. A., 841*
- Sugarman, H., Friedman, M., and Selzer, A., 844*
- Surgeon, role for, in problem of essential hypertension, 138*
- Swank, Roy L., Porter, R. R., and Yeomans, A., 154
- Sympathectomy, and occlusion, experimental, of coronary artery, 545
- chemical, prevention of ischemic gangrene following surgical operations upon major peripheral arteries by, 137*
- lumbar, in treatment of selected cases of peripheral or arteriosclerotic disease, 75
- Syphilitis, congenital, incidence of heart disease in children with, 844*
- Szekely, P., 360

T

- T waves, alterations of, caused by change of posture, 279*
- Tachycardia, auricular, paroxysmal, auricular fibrillation, following injection of acetyl- β -methylcholine chloride (mecholyl) during attack of, 425*
- complicating pregnancy, 570*
- paroxysmal, and its treatment in young infants, 282*
- ventricular, paroxysmal, favorable prognosis in absence of acute cardiac damage and its treatment with parenterally administered quinine dihydrochloride, 219
- paroxysms of, Wolff-Parkinson-White syndrome with, 401
- Talbott, John H., Coombs, F. S., Castleman, B., Chamberlain, F. L., Consolazio, W. V., and White, P. D., 754
- Taquiri, A. C., 567*
- Taylor, H. K., Galdston, M., Govons, S., Wortis, S. B., and Steele, J. M., 572*
- Teran, V. S., 425*
- Theobromine sodium acetate, tablets, enteric-coated, prolonged use of, in treatment of edema and angina pectoris, 847*
- Thiamin hydrochloride, dogs deficient in, production and study of cardiac failure in, 154
- Thompson, J. H., Aggeler, P. M., and Lucia, S. P., 825

- Thomson, K. Jefferson, and Hamilton, B. E., 431
- Thromboangiitis obliterans, coronary artery thrombosis with recovery in, 707
- spa treatment of, 180
- Thrombophlebitis, tuberculous, tuberculous peripheral arteries associated with, in lungs, 702
- Thyroid gland, hormone of, influence of, on heart and circulation, 577 (B. rev.)
- Tonsillectomy, influence of, on progress of rheumatic heart disease, 133*
- Trypanosomiasis, experimental, electrocardiogram in, 567*
- Tuberculosis of pericardium and heart, 843*
- Tung, Chen-Lang, 35
- Tuohy, E. L., Boman, P. G., and Berdez, G. L., 305
- Turner, G. G., 575*

U

- Urban, J. A., Wechsler, H. F., and Farmer, L., 280*

V

- Valve, aortic, insufficiency of, due to syphilis, study of its genesis, 569*
- lesion of, associated with Austin Flint murmur, 208
- ruptured, with mycotic aneurysm due to acute bacterial endocarditis, 426*
- stenosis, calcareous, of, report of nine cases with autopsy findings, 425
- mitral, stenosis of, after eighty, 281*
- pulmonary, stenosis of, and nodular ossification of lungs, 281*
- with bundle branch block, 280*
- Van Dellen, T. R., and Miller, J. R., 429*
- Vascular system, peripheral, responses of, to exercise in hyperthyroid state, 566*
- Vasoconstrictor reflex, relative responses of dorsal metacarpal, digital and terminal skin arteries of hand in, 574*
- Veal, J. R., and Hussey, H. H., 427*
- Veins, constriction of arteries and, effect of, induced by parendrine on lung capacity and its subdivisions, 430*
- deep, of leg, thrombosis of, its clinical significance as exemplified in three hundred and fifty-one autopsies, 574*
- femoral, ligation of, for chronic occlusive arterial disease, 428*
- pressure in (see blood pressure, venous)

Veins—Cont'd

- pulsation, systolic, generalized, significance of, with report of case in which there was marked pulsation of varicose veins, 410
- thebesian, observations on role of, and luminal vessels in right ventricle, 276*
- varicose, pulsation, systolic, marked, of, significance of generalized systolic pulsation of veins, 410
- Vena cava, superior, occlusion, constriction of, 428*
- Venous pressure (*see* blood pressure, venous)
- Ventricle, left, strain of, with and without left axis deviation, characteristic electrocardiograms in, 279*
- right, observations on role of thebesian veins and luminal vessels in, 276*
- variations in filling and output of, with phases of respiration, 561
- Vischer, M. B., and Burchell, H. B., 794
- Vitamin B therapy, treatment of Sydenham's chorea by fever, and, 426*
- Viveros, R., Garreton-Silva, A., Croxatto, R., and Fuenzalida, O., 284*

W

- Wagner, J. A., and Stroud, W. D., 841*
- Walker, George, Lalich, J., and Cohen, L., 105
- Walking, intermittent claudication as result of arterial spasm induced by, 719
- Walsh, B. J., and Sprague, H. B., 283*
- Wasmuht, K., and Bayer, O., 841*
- Wasson, Valentina P., Brown, E. E., and Weintraub, C., 342
- Water, loss of, quantitative method for measurement of rate of, from small areas, with results for finger tip, toe tip and postero-superior portion of pinna of normal resting adults, 276*
- restrictions of salt as compared with, in congestive heart failure, 141
- Wearn, J. T., 564*
- , Eckstein, R. W., Roberts, J. T., and Gregg, D. E., 276
- Wechsler, H. F., Farmer, L., and Urban, J. A., 280
- Wedd, A. M., Blair, H. A., and Dwyer, G. K., 847*
- Wégria, R., Moe, G. K., and Wiggers, C. J., 277*
- Weintraub, Clarice, Wasson, V. P., and Brown, E. E., 342
- Weir, David R., and Jones, B. C., Jr., 556
- Weiss, Morris M., 112

- Weiss, S., 278*
- Weltz, G. A., 712*
- Wenckebach, Karel Frederik, in memorandum, 852
- Wendkos, Martin H., 417
- Wendt, L., 841*
- Wenstrand, D. E. W., and Feldt, R. H., 424*
- White, P. D., and Bland, E. F., 281*
- , and Cooke, W. T., 425*
- , and Graybiel, A., 561*
- White, Paul D., Leach, C. E., and Foote, S. A., 321
- , Ruffin, M. deG., and Castleman, B., 458
- , Talbott, J. H., Coombs, F. S., Castleman, B., Chamberlain, F. L., and Consolazio, W. V., 754
- Wiesel, B. H., Schechter, A. E., and Cohn, C., 564*
- Wiggers, C. J., 276*, 714*
- , Moe, G. K., and Harris, A. S., 713*
- , Wégria, R., and Moe, G. K., 277*
- Williams, Norman E., Carr, H. A., Bruenn, H. G., and Levy, R. L., 252
- Willius, Fredrick A., and Keys, T. E., 578
- Wilson, Frank N., and Johnson, F. D., 64
- Wolf, S., and Hardy, J. D., 566*
- Wolferth, Charles C., and Wood, F. C., 450
- Wolff-Parkinson-White syndrome, with paroxysms of ventricular tachycardia, 401
- Volkin, Julius, and Hyndman, O. R., 289
- Wood, Francis C., and Wolferth, C. C., 450
- Wood, P., 286*
- Wortis, S. B., Galdston, M., Govons, S., Steele, J. M., and Taylor, H. K., 572*
- Wray, S., and Bain, C. W. C., 426*
- Wright, Irving S., Schwartz, M. S., Fisher, M. M., and Duryee, A. W., 122
- , McGovern, T., and Kruger, E., 583

X

- Xanthine compounds, effects of, further observations on, in cases of coronary insufficiency as indicated by response to induced anoxemia, 252
- drugs, effectiveness of, in treatment of angina pectoris. I. Aminophylline, 576*

Y

- Yeomans, Andrew, Swank, R. L., and Porter, R. R., 154
- Yodice, Arnaldo, 545

Z

- Zoll, P. M., Blumgart, H. L., and Schlesinger, M. J., 568

